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QUINAZOLINES WITH THERAPEUTIC USE

Abstract:

The invention concerns the use of quinazoline derivatives of Formula (I) wherein Q<1> includes a qinazoline ring optionally substituted with a group such as halogeno, trifluoromethyl and cyano, or a group of the formula: Q<3>-X<1>- wherein X<1> includes a direct bond and O and Q<3> includes aryl, aryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6)alkyl; each of R<2> and R<3> is hydrogen or (1-6C)alkyl; Z includes O, S and NH; and Q<2> includes aryl and aryl-(1-3C)alkyl or a pharmaceutically-acceptable salt thereof; in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

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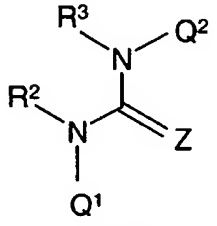

(I)

(57) Abstract: The invention concerns the use of quinazoline derivatives of Formula (I) wherein Q^1 includes a qinazoline ring optionally substituted with a group such as halogeno, trifluoromethyl and cyano, or a group of the formula: Q^3-X^1- wherein X^1 includes a direct bond and O and Q^3 includes aryl, aryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6)alkyl; each of R^2 and R^3 is hydrogen or (1-6C)alkyl; Z includes O, S and NH; and Q^2 includes aryl and aryl-(1-3C)alkyl or a pharmaceutically-acceptable salt thereof; in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

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QUINAZOLINES WITH THERAPEUTIC USE

The invention concerns a new use of certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which have been found to possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine

kinases such as the EGF, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, is frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer (Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human

tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalance will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases.

It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24 , 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

It is disclosed by K. H. Gibson *et al.*, Bioorganic & Medicinal Chemistry Letters, 1997, 7, 2723-2728 that certain 4-anilinoquinazoline derivatives possess useful EGF RTK inhibitory properties. It is also disclosed that 1-(6,7-dimethoxyquinazolin-4-yl)-3-phenylurea is inactive as an EGF RTK inhibitor.

It is disclosed in International Patent Application WO 98/50370 that certain 5-substituted quinazoline derivatives may be useful as inhibitors of serine/threonine protein kinases. Whilst most of the examples are 4-amino-5-phenoxyquinazolines, there is the disclosure of three 4-ureido-5-phenoxyquinazolines, namely of :-
1-[5-(4-methoxyphenoxy)quinazolin-4-yl]-3-phenylurea,
1-[5-(4-methoxyphenoxy)quinazolin-4-yl]-3-(3-bromophenyl)urea and
1-[5-(4-methoxyphenoxy)quinazolin-4-yl]-3-(3-methoxyphenyl)urea.

It is disclosed by C. I. Hong *et al.*, J. Med. Chem., 1976, 19, 555-558 that certain 4-aminopyrazolo[3,4-*d*]pyrimidine derivatives possess growth inhibitory activity against cultured L1210 leukaemia cells. The disclosed compounds include:-
1-phenyl-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea,
1-(2-chlorophenyl)-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea,
1-(3-chlorophenyl)-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea,
1-(4-chlorophenyl)-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea,
1-(2-fluorophenyl)-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea,
1-benzyl-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea and
1-(3-phenylpropyl)-3-(pyrazolo[3,4-*d*]pyrimidin-4-yl)urea.

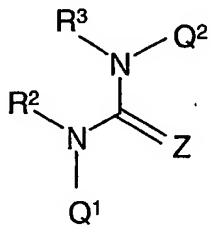
It is disclosed in International Patent Application WO 97/03069 that certain quinoline and quinazoline derivatives may be useful as protein tyrosine kinase inhibitors. All of the disclosed examples are 4-heteroarylaminoquinazoline derivatives and none of them are 1-heteroaryl-3-(quinazolin-4-yl)urea derivatives.

It is disclosed in International Patent Application WO 98/43960 that certain 3-cyanoquinoline derivatives may be useful as protein tyrosine kinase inhibitors. Almost all of the 398 disclosed examples were 3-cyano-4-anilinoquinoline or 3-cyano-4-benzylaminoquinoline derivatives. There is no disclosure of any (3-cyanoquinolin-4-yl)urea derivatives.

It is disclosed in International Patent Application WO 99/09024 that certain 1-phenyl-3-(quinolin-4-yl)urea derivatives may be useful as antagonists of the human HFGAN72 receptor, a G-protein coupled neuropeptide receptor, and hence may be of

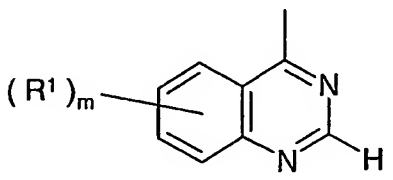
potential use in the treatment of obesity. There is no disclosure as examples of any 1-phenyl-3-(quinazolin-4-yl)urea or 1-phenyl-3-(3-cyanoquinolin-4-yl)urea compounds.

According to one aspect of the invention there is provided the use of a quinazoline derivative of the Formula I

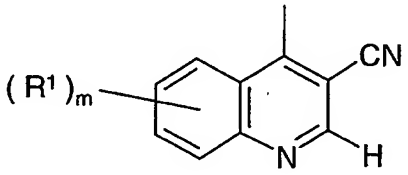


I

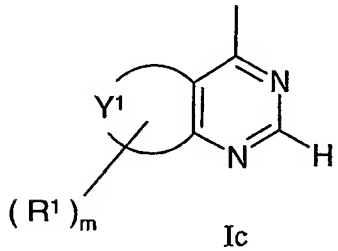
wherein $\mathbf{Q^1}$ is a quinazoline-like ring such as a group of the formula Ia, Ib, Ic or Id



Ia



Ib



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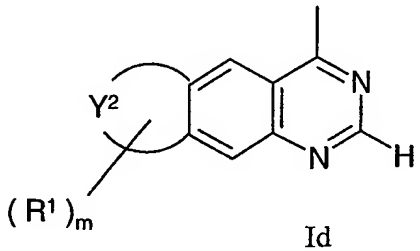


Id

wherein :

$\mathbf{Y^1}$ together with the carbon atoms to which it is attached forms a 5- or 6-membered aromatic or partially unsaturated ring comprising 1 to 3 heteroatoms selected from O, N and S;

$\mathbf{Y^2}$ together with the carbon atoms to which it is attached forms a 5- or 6-membered aromatic or partially unsaturated ring comprising 1 to 3 heteroatoms selected from O, N and S;

m is 0, 1, 2, 3 or 4;

each $\mathbf{R^1}$ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy,

(2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$Q^3-X^1-$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^4-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-

(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3-Q^5$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^6$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^6 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and any Q^6 group optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

$\mathbf{R^2}$ is hydrogen or (1-6C)alkyl and $\mathbf{R^3}$ is hydrogen or (1-6C)alkyl, or R^2 and R^3 together form a CH_2, $(CH_2)_2$ or $(CH_2)_3$ group;

Z is O, S, N(C≡N) or N(R^{11}), wherein R^{11} is hydrogen or (1-6C)alkyl; and

$\mathbf{Q^2}$ is aryl, aryl-(1-3C)alkyl, aryl-(3-7C)cycloalkyl, heteroaryl, heteroaryl-(1-3C)alkyl or heteroaryl-(3-7C)cycloalkyl wherein each aryl group is phenyl or naphthyl and each heteroaryl group is a 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic heteroaryl ring containing 1 or 2 nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulphur, and

Q^2 is optionally substituted with 1, 2, 3 or 4 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^6-R^{12}$$

wherein X^6 is a direct bond or is selected from O and N(R^{13}), wherein R^{13} is hydrogen or (1-6C)alkyl, and R^{12} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^7$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, N(R^{14}), CO, CH(OR^{14}), CON(R^{14}), N(R^{14})CO, SO_2N(R^{14}), N(R^{14})SO_2, C(R^{14})$_2$O, C(R^{14})$_2$S and C(R^{14})$_2$N(R^{14}), wherein each R^{14} is hydrogen or (1-6C)alkyl, and Q^7 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or Q^2 is optionally substituted with a (1-3C)alkylenedioxy group,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on Q^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from

halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^8-R^{15}$$

wherein X^8 is a direct bond or is selected from O and $N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and R^{15} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on Q^2 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a c-Src kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that the hydrogen atom which is shown at the 2-position in each of the part structures of the formulae Ia, Ib, Ic and Id indicates that that position remains unsubstituted by any R^1 group.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q^2 to Q^7) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for a (3-7C)cycloalkyl group within Q^2 or for Q^3 or Q^4 when it is (3-7C)cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for Q^3 or Q^4 when it is (3-7C)cycloalkenyl is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for Q^2 when it is a 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic heteroaryl ring containing 1 or 2 nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulphur is, for example, pyrrolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, indolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl, preferably isoxazolyl, 1,2,3-triazolyl, pyridyl, benzothiazolyl, quinolyl or quinazolinyl.

A suitable value for any one of the 'Q' groups, Q^3 to Q^7,when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl, preferably thienyl, 1,2,3-triazolyl, pyridyl, quinolyl, quinazolinyl or quinoxalinyl.

A suitable value for any one of the 'Q' groups, Q^3 to Q^7, when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl,

1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl or homopiperazin-1-yl, more preferably piperidin-4-yl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

When, as defined hereinbefore, Y^1 together with the carbon atoms to which it is attached forms a 5- or 6-membered aromatic or partially unsaturated ring comprising 1 to 3 heteroatoms selected from O, N and S, ring Y^1 is suitably unsaturated or partially unsaturated wherein a $-CH_2-$ group can optionally be replaced by a -CO- group and a ring nitrogen atom may optionally bear a (1-6C)alkyl group. Diradicals of suitable fused Y^1 rings include thiendiyl, furandiyl, imidazolediyl, pyrazolediyl, oxazolediyl, isoxazolediyl, thiazolediyl, isothiazolediyl, 1,2,3-oxadiazolediyl, 1,2,3-triazolediyl, pyridinediyl, pyrimidinediyl, pyrazinediyl, pyridazinediyl and 1,3,4-triazinediyl. Examples of suitable bicyclic rings of formula Ic formed by the fusion of ring Y^1 to the adjacent pyrimidine ring include furopyrimidinyl, thienopyrimidinyl, purinyl, pyrrolopyrimidinyl, pyrrolinopyrimidinyl, oxopyrrolinopyrimidinyl, oxazolopyrimidinyl, oxazolinopyrimidinyl, oxooxazolinopyrimidinyl, isoxazolopyrimidinyl, thiazolopyrimidinyl, thiazolinopyrimidinyl, oxothiazolinopyrimidinyl, isothiazolopyrimidinyl, oxoimidazolinopyrimidinyl, pyrazolopyrimidinyl, pyrazolinopyrimidinyl, oxopyrazolinopyrimidinyl, pyridopyrimidinyl, pyrimidopyrimidinyl and pteridinyl. Preferably the bicyclic ring of formula Ic is furo[3,2-*d*]pyrimidinyl, furo[2,3-*d*]pyrimidinyl, thieno[3,2-*d*]pyrimidinyl, thieno[2,3-*d*]pyrimidinyl, 6-purinyl, pyrrolo[3,2-*d*]pyrimidinyl, pyrrolo[2,3-*d*]pyrimidinyl, oxazolo[5,4-*d*]pyrimidinyl, oxazolo[4,5-*d*]pyrimidinyl, thiazolo[5,4-*d*]pyrimidinyl, thiazolo[4,5-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrido[4,3-*d*]pyrimidinyl, pyrido[3,2-*d*]pyrimidinyl, pyrimido[4,5-*d*]pyrimidinyl,

pyrimido[5,6-*d*]pyrimidinyl or pteridinyl. More specifically the bicyclic ring of formula Ic is 6-oxopyrrolino[2,3-*d*]pyrimidin-4-yl, 6-oxopyrrolino[3,2-*d*]pyrimidin-4-yl, 2-oxooxazolino[5,4-*d*]pyrimidin-7-yl, 2-oxothiazolino[5,4-*d*]pyrimidin-7-yl, 2-oxooxazolino[4,5-*d*]pyrimidin-7-yl, 2-oxothiazolino[4,5-*d*]pyrimidin-7-yl, 2-oxoimidazolino[4,5-*d*]pyrimidin-7-yl, 3-oxopyrazolino[3,4-*d*]pyrimidin-4-yl or 3-oxopyrazolino[4,3-*d*]pyrimidin-7-yl. Further preferred bicyclic rings of formula Ic include thieno[3,2-*d*]pyrimidinyl, thieno[2,3-*d*]pyrimidinyl, thiazolo[5,4-*d*]pyrimidinyl, 6-purinyl, pyrido[2,3-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrido[4,3-*d*]pyrimidinyl, pyrido[3,2-*d*]pyrimidinyl and pteridinyl, more specifically thieno[3,2-*d*]pyrimidin-4-yl, thieno[2,3-*d*]pyrimidin-4-yl, thiazolo[5,4-*d*]pyrimidin-7-yl, pyrido[2,3-*d*]pyrimidin-4-yl, pyrido[3,4-*d*]pyrimidin-4-yl, pyrido[4,3-*d*]pyrimidin-4-yl, pyrido[3,2-*d*]pyrimidin-4-yl and pteridin-4-yl.

When, as defined hereinbefore, Y^2 together with the carbon atoms to which it is attached forms a 5- or 6-membered aromatic or partially unsaturated ring comprising 1 to 3 heteroatoms selected from O, N and S, ring Y^2 is suitably unsaturated or partially unsaturated wherein a $-CH_2-$ group can optionally be replaced by a -CO- group and a ring nitrogen atom may optionally bear a (1-6C)alkyl group. Diradicals of suitable fused Y^2 rings include thiendiyl, furandiyl, imidazolediyl, pyrazolediyl, oxazolediyl, isoxazolediyl, thiazolediyl, isothiazolediyl, 1,2,3-oxadiazolediyl, 1,2,3-triazolediyl, pyridinediyl, pyrimidinediyl, pyrazinediyl, pyridazinediyl and 1,3,4-triazinediyl. Examples of suitable tricyclic rings of formula Id formed by the fusion of ring Y^2 to the adjacent quinazoline ring include imidazoquinazolinyl, oxazoloquinazolinyl, thiazoloquinazolinyl, [1,2,3]triazoloquinazolinyl, pyrazoloquinazolinyl, pyrroloquinazolinyl, oxoimidazolinoquinazolinyl, oxooxazolinoquinazolinyl, oxothiazolinoquinazolinyl and oxopyrazolinoquinazolinyl. Preferably the tricyclic ring of formula Id is 3H-imidazo[4,5-*g*]quinazolinyl, oxazolo[4,5-*g*]quinazolinyl, thiazolo[4,5-*g*]quinazolinyl, 3H-[1,2,3]triazolo[4,5-*g*]quinazolinyl, 1H-pyrazolo[3,4-*g*]quinazolinyl, 6H-pyrrolo[2,3-*g*]quinazolinyl, 2-oxo-1,2-dihydro-3H-imidazo[4,5-*g*]quinazolinyl, 2-oxo-1,2-dihydrooxazolo[4,5-*g*]quinazolinyl, 2-oxo-1,2-dihydrothiazolo[4,5-*g*]quinazolinyl, 3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*g*]quinazolinyl, pyrido[2,3-*g*]quinazolinyl, pyrimidino[4,5-*g*]cinnolinyl, pyrimidino[4,5-*g*]quinazolinyl, pyrazino[2,3-*g*]quinazolinyl, 7-oxo-6,7-dihydropyrido[2,3-*g*]quinazolinyl, pyrazino[2,3-*g*]quinazolinyl and 8-oxo-8,9-dihydropyrazino[2,3-*g*]quinazolinyl. More specifically the tricyclic ring of

formula Id is 3H-imidazo[4,5-*g*]quinazolin-8-yl, oxazolo[4,5-*g*]quinazolin-8-yl, thiazolo[4,5-*g*]quinazolin-8-yl, 3H-[1,2,3]triazolo[4,5-*g*]quinazolin-8-yl, 1H-pyrazolo[3,4-*g*]quinazolin-8-yl, 6H-pyrrolo[2,3-*g*]quinazolin-4-yl, 2-oxo-1,2-dihydro-3H-imidazo[4,5-*g*]quinazolin-8-yl, 2-oxo-1,2-dihydrooxazolo[4,5-*g*]quinazolin-8-yl, 2-oxo-1,2-dihydrothiazolo[4,5-*g*]quinazolin-8-yl, 3-oxo-2,3-dihydro-1H-pyrazolo[3,4-*g*]quinazolin-8-yl, pyrido[2,3-*g*]quinazolin-4-yl, pyrimidino[4,5-*g*]cinnolin-9-yl, pyrimidino[4,5-*g*]quinazolin-4-yl, pyrazino[2,3-*g*]quinazolin-4-yl, 7-oxo-6,7-dihydropyrido[2,3-*g*]quinazolin-4-yl, pyrazino[2,3-*g*]quinazolin-4-yl or 8-oxo-8,9-dihydropyrazino[2,3-*g*]quinazolin-4-yl. Further preferred tricyclic rings of formula Id include 3-methyl-3H-imidazo[4,5-*g*]quinazolin-8-yl, 3-methyl-3H-[1,2,3]triazolo[4,5-*g*]quinazolin-8-yl, 3-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-*g*]quinazolin-8-yl, pyrazino[2,3-*g*]quinazolin-4-yl and 9-methyl-8-oxo-8,9-dihydropyrazino[2,3-*g*]quinazolin-4-yl.

Suitable values for any of the 'R' groups (R^1 to R^{16}), or for various groups within an R^1 substituent, or within a substituent on Q^2 include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-8C)alkenyl:	vinyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for N,N-di-[(1-6C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;

for (2-6C)alkanoyl: acetyl and propionyl;

for (2-6C)alkanoyloxy: acetoxy and propionyloxy;

for (2-6C)alkanoylamino: acetamido and propionamido;

for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;

for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;

for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;

for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;

for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;

for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;

for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;

for (3-6C)alkynoylamino: propiolamido;

for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;

for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;

for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;

for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;

for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl.

A suitable value for $(R^1)_m$ or for a substituent on Q^2 when it is (1-3C)alkylenedioxy is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^3-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline-like ring such as the ring of formula Ia and the oxygen atom is attached to the Q^3 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula -X^3-Q^5 and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^5 group. A similar convention applies to the attachment of the groups of the formulae Q^4-X^2- and -X^7-Q^7.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^5)$ or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent such as a group of the formula Q^4-X^2- wherein X^2 is, for example, NHCO and Q^4 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents, there are

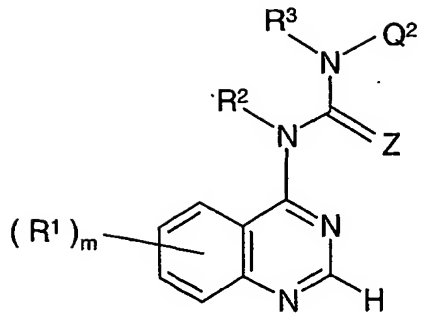
suitably 1 or 2 halogeno substituents present on each said CH_2 group and there are suitably 1, 2 or 3 halogeno substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular compounds of the Formula I include, for example,

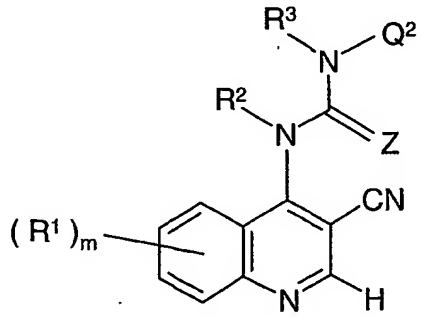
(i) quinazoline derivatives of the Formula II



II

wherein each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore;

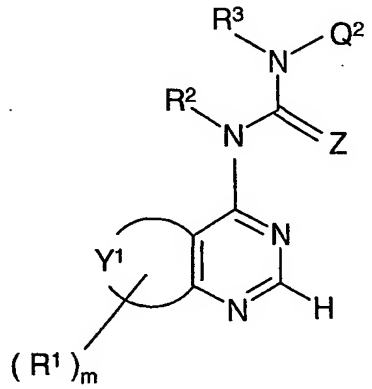
(ii) quinoline derivatives of the Formula III



III

wherein each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore;

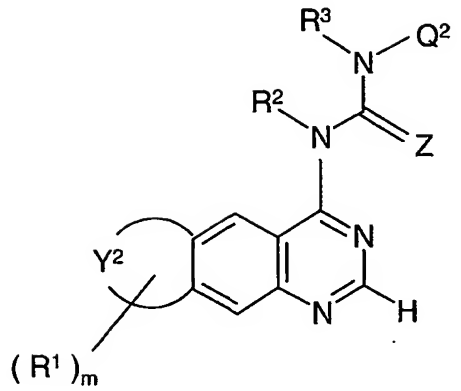
(iii) pyrimidine derivatives of the Formula IV



IV

wherein each of m, R^1, Y^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore; and

(iv) quinazoline derivatives of the Formula V



V

wherein each of m, R^1, Y^2, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore.

Further particular compounds of the Formula I include, for example, quinazoline derivatives of the Formula II, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore or in paragraphs (a) to (l) hereinafter :-

(a) m is 1, 2 or 3, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :

$$Q^3\text{-}X^1\text{-}$$

wherein X^1 is a direct bond or is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$ wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^4-X^2-$$

wherein X^2 is a direct bond or is CO or $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^4 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :

$$-X^3-Q^5$$

wherein X^3 is a direct bond or is selected from O, $N(R^7)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^5 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl and (1-6C)alkoxycarbonylamino-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(b) m is 1, 2 or 3, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

$$Q^3-X^1-$$

wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH_2 and Q^3 is phenyl, benzyl, cyclopropylmethyl, thienyl, 1-imidazolyl, 1,2,3-triazolyl, pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl, homopiperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl,

3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of the formula :

$$Q^4-X^2-$$

wherein X^2 is a direct bond or is CO, NHCO or N(Me)CO and Q^4 is pyridyl, pyridylmethyl, 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino and dimethylamino, or from a group of the formula :

$$-X^3-Q^5$$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^5 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl,

3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, aminomethyl, methylaminomethyl, dimethylaminomethyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl and tert-butoxycarbonylaminomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(c) m is 1 or 2 and the R^1 groups, which may be the same or different, are located at the 6- and/or 7-positions and are selected from hydroxy, amino, methyl, ethyl, propyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, benzyloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, piperidin-3-ylamino,

piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from

N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :

$$Q^4-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^4 is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any phenyl, pyridyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, aminomethyl, acetamidomethyl and tert-butoxycarbonylaminomethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(d) each of R^2 and R^3 is hydrogen or methyl;

(e) each of R^2 and R^3 is hydrogen;

(f) Z is O, S or $N(R^{11})$, wherein R^{11} is hydrogen or (1-6C)alkyl;

(g) Z is O, S, $N(R^{11})$, wherein R^{11} is hydrogen, methyl, ethyl or propyl;

(h) Z is O;

(i) Q^2 is phenyl, benzyl, α-methylbenzyl, phenethyl, naphthyl, 1-(1-naphthyl)ethyl or 2-phenylcyclopropyl which is optionally substituted with 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, or from a group of the formula :

$$-X^6-R^{12}$$

wherein X^6 is a direct bond or is selected from O and $N(R^{13})$, wherein R^{13} is hydrogen or (1-6C)alkyl, and R^{12} is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^7$$

wherein X^7 is a direct bond or is selected from O, $N(R^{14})$, CO, $CON(R^{14})$, $N(R^{14})CO$ and $C(R^{14})_2O$, wherein each R^{14} is hydrogen or (1-6C)alkyl, and Q^7 is phenyl, benzyl, heteroaryl or heteroaryl-(1-6C)alkyl,

and wherein any phenyl or heteroaryl group within a substituent on Q^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, (1-6C)alkyl and (1-6C)alkoxy;

(j) Q^2 is phenyl, benzyl, α-methylbenzyl or phenethyl which is optionally substituted with 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, cyano, nitro, hydroxy, methyl, ethyl, propyl, tert-butyl, vinyl, ethynyl and methoxy, or from a group of the formula :

$$-X^7-Q^7$$

wherein X^7 is a direct bond or is selected from O and CO, and Q^7 is phenyl, benzyl, pyridyl or pyridylmethyl, and wherein any phenyl or pyridyl group within a substituent on Q^2 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl and methoxy;

(k) Q^2 is phenyl, benzyl or phenethyl which is substituted with 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, cyano, nitro, hydroxy, methyl, ethyl, propyl, tert-butyl, vinyl, ethynyl and methoxy provided that at least one substituent is located at an ortho position (for example the 2-position on a phenyl group); and

(l) Q^2 is phenyl, benzyl or phenethyl which is substituted with 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, cyano, nitro, hydroxy, methyl, ethyl, propyl, tert-butyl, vinyl, ethynyl and methoxy provided that two substituents are located at ortho positions (for example the 2- and 6-positions on a phenyl group).

Further particular compounds of the Formula I include, for example, quinoline derivatives of the Formula III, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore or in any of the paragraphs (a) to (o) immediately hereinbefore.

Further particular compounds of the Formula I include, for example, pyrimidine derivatives of the Formula IV, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore or in any of the paragraphs (a) to (l) immediately hereinbefore and Y^1 has any of the meanings defined hereinbefore or in paragraphs (a) to (c) hereinafter :-

(a) bicyclic rings formed by the fusion of ring Y^1 to the adjacent pyrimidine ring include thieno[3,2-*d*]pyrimidin-4-yl, thieno[2,3-*d*]pyrimidin-4-yl, thiazolo[5,4-*d*]pyrimidin-7-yl, pyrido[2,3-*d*]pyrimidin-4-yl, pyrido[3,4-*d*]pyrimidin-4-yl, pyrido[4,3-*d*]pyrimidin-4-yl and pyrido[3,2-*d*]pyrimidin-4-yl;

(b) bicyclic rings formed by the fusion of ring Y^1 to the adjacent pyrimidine ring include thieno[3,2-*d*]pyrimidin-4-yl, pyrido[3,4-*d*]pyrimidin-4-yl, pyrido[4,3-*d*]pyrimidin-4-yl and pyrido[3,2-*d*]pyrimidin-4-yl; and

(c) the bicyclic ring formed by the fusion of ring Y^1 to the adjacent pyrimidine ring is thieno[3,2-*d*]pyrimidin-4-yl.

Further particular compounds of the Formula I include, for example, quinazoline derivatives of the Formula V, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined hereinbefore or in any of the paragraphs (a) to (l) immediately hereinbefore and Y^2 has any of the meanings defined hereinbefore or in paragraphs (a) and (b) hereinafter :-

(a) tricyclic rings formed by the fusion of ring Y^2 to the adjacent quinazoline ring include 3H-imidazo[4,5-*g*]quinazolin-8-yl and 2-oxo-1,2-dihydro-3H-imidazo[4,5-*g*]quinazolin-8-yl; and

(b) tricyclic rings formed by the fusion of ring Y^2 to the adjacent quinazoline ring include 3-methyl-3H-imidazo[4,5-*g*]quinazolin-8-yl and 3-methyl-2-oxo-1,2-dihydro-3H-imidazo[4,5-*g*]quinazolin-8-yl.

A further particular compound of the invention is a quinazoline derivative of the Formula II wherein :

m is 1 and the R^1 group is located at the 6- or 7-position and is selected from methoxy, benzyloxy, cyclopropylmethoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, N-methylpyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 2-(N-methylpyrrolidin-2-yl)ethoxy, 3-pyrrolidin-2-ylpropoxy, 3-(N-methylpyrrolidin-2-yl)propoxy, 2-(2-oxoimidazolidin-1-yl)ethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-(4-aminomethylpiperidin-1-yl)propoxy, 3-(4-tert-butoxycarbonylaminopiperidin-1-yl)propoxy, 3-(4-carbamoylpiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-1-yloxy, 2-(2-morpholinoethoxy)ethoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy, 3-[N-(2-methoxyethyl)-N-methylamino]propoxy, 2-(2-methoxyethoxy)ethoxy, 3-methylamino-1-propynyl, 3-dimethylamino-1-propynyl, 3-diethylamino-1-propynyl, 6-methylamino-1-hexynyl, 6-dimethylamino-1-hexynyl, 3-(pyrrolidin-1-yl)-1-propynyl, 3-(piperidino)-1-propynyl, 3-(morpholino)-1-propynyl, 3-(4-methylpiperazin-1-yl)-1-propynyl,

6-(pyrrolidin-1-yl)-1-hexynyl, 6-(piperidino)-1-hexynyl, 6-(morpholino)-1-hexynyl, 6-(4-methylpiperazin-1-yl)-1-hexynyl, piperazin-1-yl, 4-methylpiperazin-1-yl, 3-imidazol-1-ylpropylamino, 3-pyrrolidin-1-ylpropylamino, 3-morpholinopropylamino, 3-piperidinopropylamino and 3-piperazin-1-ylpropylamino,

or m is 2 and the R^1 groups are located at the 6- and 7-positions, one R^1 group is located at the 6- or 7-position and is selected from the groups defined immediately hereinbefore and the other R^1 group is a methoxy group;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O, S, NH or N(Et); and

Q^2 is phenyl, benzyl or phenethyl which optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl and methoxy provided that at least one substituent is located at an ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula II

wherein :

m is 1 or 2 and the R^1 groups, which may be the same or different, are located at the 6- and/or 7-positions and are selected from methoxy, benzyloxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, 1-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 1-methylpyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 2-(1-methylpyrrolidin-2-yl)ethoxy, 3-pyrrolidin-2-ylpropoxy, 3-(1-methylpyrrolidin-2-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, 1-methylpiperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(1-methylpiperidin-3-yl)ethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-

1-yloxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy and 3-[N-(2-methoxyethyl)-N-methylamino]propoxy;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O; and

Q^2 is phenyl, benzyl or phenethyl which optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl and methyl; or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula II wherein :

m is 1 and the R^1 group is located at the 7-position and is selected from 3-(1,2,3-triazol-1-yl)propoxy, 2-pyrid-4-ylethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-pyrrolidin-1-ylbut-2-en-1-yloxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-1-yloxy, 3-methylsulphonylpropoxy and 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy;

or m is 2 and one R^1 group is located at the 7-position and is selected from the groups defined immediately hereinbefore and the other R^1 group is a 6-methoxy group;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O, S, NH or N(Et); and

Q^2 is phenyl which bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl and methoxy provided that at least one substituent is located at an ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of the Formula II wherein :

m is 1 and the R^1 group is located at the 7-position and is selected from 3-(1,2,3-triazol-1-yl)propoxy, 2-pyrid-4-ylethoxy, 3-pyrrolidin-1-ylpropoxy,

3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, N-methylpiperidin-4-ylmethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-1-yloxy, 3-methylsulphonylpropoxy and 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy;

or m is 2 and one R^1 group is located at the 7-position and is selected from the groups defined immediately hereinbefore and the other R^1 group is a 6-methoxy group;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O; and

Q^2 is phenyl which bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo and trifluoromethyl provided that at least one substituent is located at an ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is, for example, a quinazoline derivative of the Formula II selected from :-

1-(2,6-dichlorophenyl)-3-[7-(3-morpholinopropoxy)quinazolin-4-yl]urea,

1-(2,6-dichlorophenyl)-3-{7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazolin-4-yl}urea,

1-benzyl-3-[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea,

1-phenethyl-3-[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea,

1-(2,6-dichlorophenyl)-3-[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea,

1-(2,6-difluorophenyl)-3-[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea,

1-(2,6-dimethylphenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea,

1-(2-chloro-6-methylphenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea,

1-(2,6-difluorophenyl)-3-[6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl]urea,

1-(2,6-difluorophenyl)-3-[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl]urea,

1-(2,6-dimethylphenyl)-3-[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl]urea,

1-(2,6-dimethylphenyl)-3-[6-methoxy-7-(3-piperidinopropoxy)quinazolin-4-yl]urea,

1-(2,6-dimethylphenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]thiourea and

1-(2-chloro-6-methylphenyl)-3-[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]guanidine;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula IV wherein the fusion of ring Y^1 to the adjacent pyrimidine ring forms a thieno[3,2-*d*]pyrimidin-4-yl group;

m is 0, or m is 1 and the R^1 group is a methyl, ethyl, vinyl or ethynyl group which is located at the 6-position and bears a substituent selected from carboxy, carbamoyl, N-(2-methylaminoethyl)carbamoyl, N-(2-dimethylaminoethyl)carbamoyl, N-(3-methylaminopropyl)carbamoyl or N-(3-dimethylaminopropyl)carbamoyl, or from a group of the formula :

$$Q^4\text{-}X^2\text{-}$$

wherein X^2 is NHCO or N(Me)CO and Q^4 is 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-pyridylmethyl, 4-pyridylmethyl, 2-pyrid-2-ylethyl, 2-pyrrolidin-1-ylethyl, 2-(2-oxopyrrolidin-1-yl)ethyl, 3-pyrrolidin-1-ylpropyl, 3-(2-oxopyrrolidin-1-yl)propyl, pyrrolidin-2-ylmethyl, 1-methylpyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 2-(1-methylpyrrolidin-2-yl)ethyl, 3-pyrrolidin-2-ylpropyl, 3-(1-methylpyrrolidin-2-yl)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 1-methylpiperidin-3-ylmethyl, 2-piperidin-3-ylethyl, 2-(1-methylpiperidin-3-yl)ethyl, piperidin-4-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-(1-methylpiperidin-4-yl)ethyl, 2-piperazin-1-ylethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-piperazin-1-ylpropyl or 3-(4-methylpiperazin-1-yl)propyl,

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O; and

Q^2 is phenyl, benzyl or phenethyl which optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl and methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula IV wherein the fusion of ring Y^1 to the adjacent pyrimidine ring forms a thieno[3,2-*d*]pyrimidin-4-yl group;

m is 0, or m is 1 and the R^1 group is a vinyl group located at the 6-position which bears at the terminal CH_2= position a substituent selected from N-(2-dimethylaminoethyl)carbamoyl or N-(3-dimethylaminopropyl)carbamoyl, or from a group of the formula :

$$Q^4-X^2-$$

wherein X^2 is NHCO or N(Me)CO and Q^4 is 2-pyridylmethyl, 4-pyridylmethyl, 2-pyrid-2-ylethyl, 2-pyrrolidin-1-ylethyl, 3-(2-oxopyrrolidin-1-yl)propyl, 3-morpholinopropyl, 2-piperidinoethyl or 3-(4-methylpiperazin-1-yl)propyl,

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O; and

Q^2 is phenyl which bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo and trifluoromethyl provided that at least one substituent is located at the ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

A particular compound of this aspect of the invention is, for example, a pyrimidine derivative of the Formula IV selected from:-

1-(2,6-dichlorophenyl)-3-(thieno[3,2-*d*]pyrimidin-4-yl)urea and

(*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}-N-(3-dimethylaminopropyl)acrylamide;

or a pharmaceutically-acceptable acid-addition salt thereof.

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are illustrated by the following representative process variants in which, unless otherwise stated, Q^1, R^2, Z, R^3 and Q^2 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) For those compounds of the Formula I wherein R^3 is hydrogen and Z is oxygen, the reaction, conveniently in the presence of a suitable base, of an amine of the Formula VI

Q^1-NHR^2 VI

wherein Q^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an isocyanate of the Formula VII, or a conventional chemical equivalent thereof or a conventional chemical precusor thereof,

$O=C=N-Q^2$ VII

wherein Q^2 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, alkoxide or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium ethoxide, potassium tert-butoxide, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal hydride, for example sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium or a dialkylamino-lithium, for example lithium di-isopropylamide.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, or a dipolar aprotic solvent such as acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 75°C.

A suitable conventional chemical equivalent of an isocyanate of the Formula VII is, for example, a compound of the Formula VIII

L-CO-NH-Q^2 VIII

wherein Q^2 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, and L is a suitable displaceable or leaving group. On treatment with a suitable base as defined hereinbefore, the compound of the Formula VIII reacts to form the desired isocyanate of the Formula VII.

A suitable displaceable or leaving group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

A suitable conventional chemical precursor of an isocyanate of the Formula VII is, for example, an acyl azide of the Formula IX

$$N_3\text{-}CO\text{-}Q^2 \qquad IX$$

wherein Q^2 has any of the meanings defined hereinbefore except that any functional group is protected if necessary. On thermal or photolytic treatment the acyl azide of the Formula IX decomposes and rearranges to form the desired isocyanate of the Formula VII.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy-lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green et al., also published by John Wiley & Son, for general guidance on protecting groups.

When L is, for example, a chloro group, the compound of the Formula VIII may be prepared by, for example, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of phosgene with an amine of the Formula X.

$$H_2N\text{-}Q^2 \qquad X$$

The compound of the Formula IX may be prepared by, for example, the reaction of a metal azide such as sodium azide with a compound of the Formula XI.

$$L\text{-}CO\text{-}Q^2 \qquad XI$$

(b) For those compounds of the Formula I wherein R^3 is hydrogen and Z is sulphur, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of an amine of the Formula VI

Q^1-NHR^2 VI

wherein Q^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an isothiocyanate of the Formula XII, or a conventional chemical equivalent thereof or a conventional chemical precusor thereof,

$S=C=N-Q^2$ XII

wherein Q^2 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable conventional chemical equivalent of an isothiocyanate of the Formula XII is, for example, a compound of the Formula XIII

L-CS-NH-Q^2 XIII

wherein Q^2 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, and L is a suitable displaceable group as defined hereinbefore. On treatment with a suitable base as defined hereinbefore, the compound of the Formula XIII reacts to form the desired isothiocyanate of the Formula XII.

A suitable conventional chemical precursor of an isothiocyanate of the Formula XII is, for example, an acyl azide of the Formula XIV

N_3-CS-Q^2 XIV

wherein Q^2 has any of the meanings defined hereinbefore except that any functional group is protected if necessary. On thermal or photolytic treatment the thioacyl azide of the Formula XIV decomposes and rearranges to form the desired isothiocyanate of the Formula XII.

When L is, for example, a chloro group, the compound of the Formula XIII may be prepared by, for example, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of thiophosgene with an amine of the Formula X.

H_2N-Q^2 X

The compound of the Formula XIV may be prepared by, for example, the reaction of a metal azide such as sodium azide with a compound of the Formula XV.

L-CS-Q^2 XV

(c) For those compounds of the Formula I wherein R^2 is hydrogen and Z is oxygen, the reaction, conveniently in the presence of a suitable base, of an amine of the Formula XVI

R^3NH-Q^2 XVI

wherein Q^2 and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an isocyanate of the Formula XVII, or a conventional chemical equivalent thereof or a conventional chemical precusor thereof,

$$Q^1\text{-}N{=}C{=}O \qquad \text{XVII}$$

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable conventional chemical equivalent of an isocyanate of the Formula XVII is, for example, a compound of the Formula XVIII

$$Q^1\text{-}NH\text{-}CO\text{-}L \qquad \text{XVIII}$$

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, and L is a suitable displaceable group as defined hereinbefore. On treatment with a suitable base as defined hereinbefore, the compound of the Formula XVIII reacts to form the desired isocyanate of the Formula XVII.

A suitable conventional chemical precursor of an isocyanate of the Formula XVII is, for example, an acyl azide of the Formula XIX

$$Q^1\text{-}CO\text{-}N_3 \qquad \text{XIX}$$

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary. On thermal or photolytic treatment the thioacyl azide of the Formula XIX decomposes and rearranges to form the desired isocyanate of the Formula XVII.

When L is, for example, a chloro group, the compound of the Formula XVIII may be prepared by, for example, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of phosgene with an amine of the Formula XX.

$$Q^1\text{-}NH_2 \qquad \text{XX}$$

The compound of the Formula XIX may be prepared by, for example, the reaction of a metal azide such as sodium azide with a compound of the Formula XXI.

$$Q^1\text{-}CO\text{-}L \qquad \text{XXI}$$

(d) For those compounds of the Formula I wherein R^2 is hydrogen and Z is sulphur, the reaction, conveniently in the presence of a suitable base, of an amine of the Formula XVI

$$R^3NH\text{-}Q^2 \qquad \text{XVI}$$

wherein Q^2 and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an isothiocyanate of the Formula XXII, or a conventional chemical equivalent thereof or a conventional chemical precusor thereof,

Q^1-N=C=S XXII

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable conventional chemical equivalent of an isothiocyanate of the Formula XXII is, for example, a compound of the Formula XXIII

Q^1-NH-CS-L XXIII

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary, and L is a suitable displaceable group as defined hereinbefore. On treatment with a suitable base as defined hereinbefore, the compound of the Formula XXIII reacts to form the desired isothiocyanate of the Formula XXII.

A suitable conventional chemical precursor of an isothiocyanate of the Formula XXII is, for example, an acyl azide of the Formula XXIV

Q^1-CS-N_3 XXIV

wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary. On thermal or photolytic treatment the thioacyl azide of the Formula XXIV decomposes and rearranges to form the desired isothiocyanate of the Formula XXII.

When L is, for example, a chloro group, the compound of the Formula XXIII may be prepared by, for example, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of thiophosgene with an amine of the Formula XX.

Q^1-NH_2 XX

The compound of the Formula XXIV may be prepared by, for example, the reaction of a metal azide such as sodium azide with a compound of the Formula XXV.

Q^1-CS-L XXV

(e) For those compounds of the Formula I wherein a substituent on Q^1 or Q^2 contains an alkylcarbamoyl group or a substituted alkylcarbamoyl group, the reaction of the corresponding compound of Formula I wherein a substituent on Q^1 or Q^2 is a carboxy group, or a reactive derivative thereof, with an amine or substituted amine as appropriate.

A suitable reactive derivative of a compound of Formula I wherein a substituent on Q^1 or Q^2 is a carboxy group is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a

chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester formed by the reaction of the acid and an ester such as pentafluorophenyl trifluoroacetate or an ester formed by the reaction of the acid and an alcohol such as N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

The reaction is conveniently carried out in the presence of a suitable base as defined hereinbefore and in the presence of a suitable inert solvent or diluent as defined hereinbefore.

Typically a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°C, typically at ambient temperature of about 20°C.

A compound of Formula I wherein a substituent on Q^1 or Q^2 is a carboxy group may conveniently be prepared by the cleavage of the corresponding ester such as a (1-12C)alkyl ester, for example by acid-, base- metal- or enzymatically-catalysed cleavage.

(f) For those compounds of the Formula I wherein a substituent on Q^1 or Q^2 contains an amino-(1-6C)alkyl group, the cleavage of the corresponding compound of Formula I wherein a substituent on Q^1 or Q^2 is a protected amino-(1-6C)alkyl group.

Suitable protecting groups for an amino-(1-6C)alkyl group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxycarbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis.

(g) For those compounds of the Formula I wherein Z is a $N(R^{11})$ group wherein R^{11} is hydrogen or (1-6C)alkyl, the reaction, conveniently in the presence of a suitable metallic salt catalyst, of a thiourea of the Formula I wherein Q^1, Q^2, R^2 and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary and Z is sulphur, with an amine of formula $R^{11}NH_2$, whereafter any protecting group that is present is removed by conventional means.

A suitable metallic salt catalyst is, for example, a mercuric salt such as mercuric(II) oxide and the reaction is conveniently carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore.

(h) For those compounds of the Formula I wherein a substituent on Q^1 or Q^2 contains an amino group, the reduction of a corresponding compound of Formula I wherein a substituent on Q^1 or Q^2 contains a nitro group.

Typical reaction conditions include the use of ammonium formate or hydrogen gas in the presence of a catalyst, for example a metallic catalyst such as palladium-on-carbon. Alternatively a dissolving metal reduction may be carried out, for example using iron in the presence of an acid, for example an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric or acetic acid. The reaction is conveniently carried out in the presence of an organic solvent (preferably a polar protic solvent) and preferably with heating, for example to about 60°C. Any functional groups are protected and deprotected as necessary.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds of the Formula I as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(a) In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa assay.

A substrate solution [100µl of a 20µg/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum Albumin (BSA; 150µl of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The

assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25µl) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40µM) was added to all test wells except the "blank" control wells which contained magnesium chloride without ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the reactions, aliquots (50µl) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100µl) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100µl) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100µl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was

approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5 x 10^4 cells per well into 96-well tissue-culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20µl) were added to each well to give a final concentration of 10µM). The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturating solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and the wells were washed with PBS (200µl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100µl) of the resultant solution was added to each well. The plates were were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer

Mannheim Catalogue No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC_{50} value was derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose (Difco Catalogue No. 0142-01) was warmed to 37°C in a waterbath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No. ATCC CCL185) were suspended at a concentration of 2×10^7 cells/ml in the medium and maintained at a temperature of 37°C.

A droplet (2µl) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the gelling of the agarose-cantaining droplets. Aliquots (90µl) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO_2 : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC_{50} was derived by plotting the mean migration measurement against test compound concentration.

(d) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5×10^6 A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a

theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (b):- IC_{50} in the range, for example, 0.01 - 20 μM;

Test (c):- activity in the range, for example, 0.1-25 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day;.

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

A pharmaceutical composition for the compounds of the Formula I comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the

particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate cell motility which is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinazoline derivatives of the Formula I possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Accordingly the quinazoline derivatives of the Formula I are of value as anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. Particularly, the quinazoline derivatives of the Formula I are of value as anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the Formula I are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor tyrosine kinases such as c-

Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the compounds of the Formula I are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the Formula I are expected to be useful in the prevention or treatment of solid tumour disease.

The anti-invasive treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrazole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated :-

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck

Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are given for illustration only and are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

Example 1 1-(2,6-dichlorophenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea

2,6-Dichlorophenyl isocyanate (0.075 g) was added to a solution of 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (0.093 g) in a mixture of methylene chloride (2 ml) and DMF (0.1 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The resultant solid was isolated, redissolved in a 20:1 mixture of methylene chloride and methanol and purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, methanol and a 1% aqueous ammonium hydroxide solution as eluent. There was thus obtained the title compound as a white solid (0.029 g); NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.7-1.8 (m, 4H), 1.85 (t, 1H), 2.1 (s, 3H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (br d, 2H), 7.3 (br s, 1H), 7.4 (d, 1H), 7.5 (s, 1H), 7.6 (s, 1H), 8.0 (br s, 1H), 8.7 (s, 1H); Mass Spectrum: $M+H^+$ 490, 492 and 494.

The 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml) which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: ($CDCl_3$) 1.25 (t, 3H), 1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: ($CDCl_3$) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a solid residue which was dissolved in diethyl ether. The organic solution was washed in turn with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g), NMR Spectrum: ($CDCl_3$) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

A portion (40 g) of the material so obtained was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6 g) and potassium carbonate (28 g) in DMF (200 ml) and the resultant mixture was stirred and heated to 95°C for 2.5 hours. The mixture was cooled to ambient temperature and partitioned between water and a mixture of ethyl acetate and diethyl ether. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The resulting oil was crystallised from petroleum ether (b.p. 60-80°C) and the suspension was stored overnight at 5°C. The resultant solid was collected by filtration, washed with petroleum ether and dried under vacuum. There was thus obtained ethyl 4-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-3-methoxybenzoate (35 g), m.p. 81-83°C; NMR Spectrum: ($CDCl_3$) 1.2-1.35 (m, 2H), 1.4 (t, 3H), 1.48 (s, 9H), 1.8-1.9 (d, 2H), 2.0-2.15 (m, 2H), 2.75 (t, 2H), 3.9 (d, 2H), 3.95 (s, 3H), 4.05-4.25 (br s, 2H), 4.35 (q, 2H), 6.85 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H).

The material so obtained was dissolved in formic acid (35 ml), formaldehyde (12M, 37% in water, 35 ml) was added and the mixture was stirred and heated to 95°C for 3 hours. The resultant mixture was evaporated. The residue was dissolved in methylene chloride and hydrogen chloride (3M solution in diethyl ether; 40 ml) was added. The mixture was diluted with diethyl ether and the mixture was triturated until a solid was formed. The solid was collected, washed with diethyl ether and dried under vacuum overnight at 50°C. There was thus obtained ethyl 3-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (30.6 g),

NMR Spectrum: ($DMSOd_6$) 1.29 (t, 3H), 1.5-1.7 (m, 2H), 1.95 (d, 2H), 2.0-2.15 (br s, 1H), 2.72 (s, 3H), 2.9-3.1 (m, 2H), 3.35-3.5 (br s, 2H), 3.85 (s, 3H), 3.9-4.05 (br s, 2H), 4.3 (q, 2H), 7.1 (d, 1H), 7.48 (s, 1H), 7.6 (d, 1H).

The material so obtained was dissolved in methylene chloride (75 ml) and the solution was cooled in an ice-bath to 0-5°C. Trifluoroacetic acid (37.5 ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming nitric acid (24M; 7.42 ml) in methylene chloride (15 ml). The resultant solution was allowed to warm to ambient temperature and was stirred for 2 hours. Volatile materials were evaporated. The residue was dissolved in methylene chloride (50 ml) and the solution was cooled in an ice-bath to 0-5°C. Diethyl ether was added and the resultant precipitate was collected and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500 ml) and hydrogen chloride (3M solution in diethyl ether; 30 ml) was added followed by diethyl ether (500 ml). The resultant solid was collected and dried under vacuum at 50°C. There was thus obtained ethyl 5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)-2-nitrobenzoate (28.4 g), NMR Spectrum: ($DMSOd_6$) 1.3 (t, 3H), 1.45-1.65 (m, 2H), 1.75-2.1 (m, 3H), 2.75 (s, 3H), 2.9-3.05 (m, 2H), 3.4-3.5 (d, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 4.3 (q, 2H), 7.32 (s, 1H), 7.66 (s, 1H).

A mixture of a portion (3.89 g) of the material so obtained, 10% platinum-on-activated carbon (50% wet, 0.389 g) and methanol (80 ml) was stirred under 1.8 atmospheres pressure of hydrogen until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30 ml) and basified to pH10 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was diluted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic layer was separated. The aqueous layer was further extracted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic extracts were combined, washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of petroleum ether (b.p. 60-80°C) and diethyl ether. The solid so obtained was isolated, washed with petroleum ether and dried under vacuum at 60°C. There was thus obtained ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (2.58 g), m.p. 111-112°C; NMR Spectrum: ($CDCl_3$) 1.35 (t, 3H), 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (t, 2H), 2.29 (s, 3H), 2.9 (d, 2H), 3.8 (s, 3H), 3.85 (d, 2H), 4.3 (q, 2H), 5.55 (br s, 2H), 6.13 (s, 1H), 7.33 (s, 1H).

A mixture of ethyl 2-amino-5-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (16.1 g), formamidine acetic acid salt (5.2 g) and 2-methoxyethanol (160 ml) was stirred and heated at 115°C for 2 hours. Further formamidine acetic acid salt (10.4 g) was added in

portions every 30 minutes during 4 hours and heating was continued for 30 minutes after the last addition. The resultant mixture was evaporated. The solid residue was stirred under a mixture of methylene chloride (50ml) and ethanol (100ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The resultant suspension was cooled to 5°C. The solid so obtained was collected, washed with cold ethanol and with diethyl ether and dried under vacuum at 60°C. There was thus obtained 6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7 g); NMR Spectrum: ($DMSOd_6$) 1.25-1.4 (m, 2H), 1.75 (d, 2H), 1.9 (t, 1H), 1.9 (s, 3H), 2.16 (s, 2H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.97 (s, 1H).

A mixture of a portion (2.8 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.28 ml) was heated to reflux for 1 hour. The mixture was evaporated and the precipitate was triturated under diethyl ether. The resultant solid was isolated and washed with diethyl ether. The solid was then dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (2.9 g,), NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H), 1.75-1.9 (m, 4H), 2.0 (t, 1H), 2.25 (s, 3H), 2.85 (d, 2H), 4.02 (s, 3H), 4.12 (d, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

A mixture of 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (11.17 g), 4-bromo-2-fluorophenol (4.57 ml), potassium carbonate (7.19 g) and DMF (110 ml) was stirred and heated at 100°C for 2.5 hours. The mixture was allowed to cool to ambient temperature and was poured into a mixture (1L) of ice and water. The precipitate was collected, washed with water and dried. The solid was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, methanol and a 1% aqueous ammonium hydroxide solution (20:1:0 to 10:1:0 to 10:1:1) as eluent. There was thus obtained 4-(4-bromo-2-fluorophenoxy)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (13.1 g), NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.7-1.8 (m, 4H), 1.9 (t, 1H), 2.15 (s, 3H), 2.5 (br s, 2H), 4.0 (s, 3H), 4.1 (d, 2H), 7.4 (s, 1H), 7.45-7.6 (m, 3H), 7.8 (d, 1H), 8.5 (s, 1H); Mass Spectrum: $M+H^+$ 476 and 478.

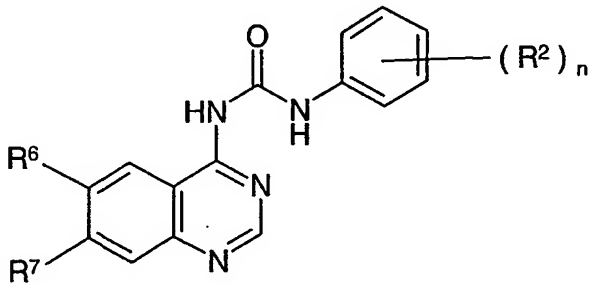
A portion (9.4 g) of the material so obtained was dissolved in a 2M solution of ammonia in isopropanol (150 ml). Liquid ammonia (10 ml) was added and the reaction mixture was sealed in a Carius tube. The reaction mixture was heated to 130°C for 16 hours. The Carius tube was cooled and opened and the reaction mixture was evaporated. The residue

was stirred under a 2N aqueous sodium hydroxide solution for 1 hour. The resultant solid was isolated and washed in turn with water and methyl tert-butyl ether. There was thus obtained 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (5.55 g); NMR Spectrum: ($DMSOd_6$) 1.2-1.4 (m, 2H), 1.7-1.8 (m, 4H), 1.85 (t, 1H), 2.1 (s, 3H), 2.8 (d, 2H), 3.8 (s, 3H), 3.9 (d, 2H), 7.0 (s, 1H), 7.3 (br s, 2H), 7.5 (s, 1H), 8.2 (s, 1H); Mass Spectrum: $M+H^+$ 303.

Example 2

Using an analogous procedure to that described in Example 1, except that, unless otherwise stated, chloroform was used in place of methylene chloride as the reaction solvent, the appropriate 4-aminoquinazoline was reacted with the appropriate isocyanate to give the compounds described in Table I. In general, unless otherwise stated, the appropriate isocyanates were commercially available. Alternatively appropriate isocyanates could be prepared by the reaction of the appropriate aniline with di-tert-butyl dicarbonate in the presence of 4-dimethylaminopyridine and a solvent such as methylene chloride.

Table I



No.	R^6	R^7	$(R^2)_n$	Note
1	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro	[1]
2	methoxy	N-methylpiperidin-4-ylmethoxy	2,3-dichloro	[2]
3	methoxy	N-methylpiperidin-4-ylmethoxy	2,4-dichloro	[3]
4	methoxy	N-methylpiperidin-4-ylmethoxy	2-fluoro	[4]
5	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-difluoro	[5]
6	methoxy	N-methylpiperidin-4-ylmethoxy	2-bromo	[6]
7	methoxy	N-methylpiperidin-4-ylmethoxy	2-trifluoromethyl	[7]
8	methoxy	N-methylpiperidin-4-ylmethoxy	2-methyl	[8]
9	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-dimethyl	[9]

10	methoxy	N-methylpiperidin-4-ylmethoxy	2-tert-butyl	[10]
11	methoxy	3-piperidinopropoxy	2,6-dimethyl	[11]
12	hydrogen	3-morpholinopropoxy	2,6-dichloro	[12]
13	hydrogen	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	2,6-dichloro	[13]
14	hydrogen	4-morpholinobut-2-ynyloxy	2,6-dichloro	[14]
15	hydrogen	(*E*)-4-morpholinobut-2-enyloxy	2,6-dichloro	[15]
16	methoxy	2-piperidinoethoxy	2,6-dichloro	[16]
17	methoxy	3-morpholinopropoxy	2,6-dichloro	[17]
18	methoxy	3-(4-methylpiperazin-1-yl)propoxy	2,6-dichloro	[18]
19	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-dichloro	[19]
20	methoxy	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	2,6-dichloro	[20]
21	methoxy	2-[N-(2-methoxyethyl)-N-methylamino]ethoxy	2,6-dichloro	[21]
22	methoxy	3-mesylpropoxy	2,6-dichloro	[22]
23	methoxy	3-(1,2,3-triazol-1-yl)propoxy	2,6-dichloro	[23]
24	methoxy	2-(4-pyridyl)ethoxy	2,6-dichloro	[24]
25	methoxy	N-methylpiperidin-4-ylmethoxy	2,4,6-trichloro	[25]
26	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-dichloro	[26]
27	methoxy	N-methylpiperidin-4-ylmethoxy	2,4-difluoro	[27]
28	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-dimethoxy	[28]
29	methoxy	N-methylpiperidin-4-ylmethoxy	2,4-dimethoxy	[29]
30	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-diisopropyl	[30]
31	methoxy	N-methylpiperidin-4-ylmethoxy	2,4,6-trimethyl	[31]
32	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-dimethyl	[32]
33	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-diethyl	[33]
34	methoxy	N-methylpiperidin-4-ylmethoxy	2-ethyl-6-methyl	[34]
35	methoxy	N-methylpiperidin-4-ylmethoxy	4-bromo-2,6-dimethyl	[35]
36	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro-6-methyl	[36]
37	methoxy	3-pyrrolidin-1-ylpropoxy	2,4,6-trichloro	[37]

38	methoxy	3-(4-methylpiperazin-1-yl)propoxy	2,4,6-trichloro	[38]
39	methoxy	3-piperidinopropoxy	2,6-dichloro	[39]
40	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-difluoro	[40]
41	methoxy	3-piperidinopropoxy	2,6-difluoro	[41]
42	methoxy	3-morpholinopropoxy	2,6-difluoro	[42]
43	methoxy	3-(4-methylpiperazin-1-yl)propoxy	2,6-difluoro	[43]
44	methoxy	2-piperidinoethoxy	2,6-difluoro	[44]
45	methoxy	2-piperidinoethoxy	2,4,6-trichloro	[45]
46	methoxy	3-pyrrolidin-1-ylpropoxy	2-fluoro-6-trifluoromethyl	[46]
47	methoxy	2-dimethylaminoethoxy	2,6-difluoro	[47]
48	methoxy	2-dimethylaminoethoxy	2,6-dichloro	[48]
49	methoxy	2-(2-oxoimidazolidin-1-yl)ethoxy	2,6-difluoro	[49]
50	methoxy	2-(2-oxoimidazolidin-1-yl)ethoxy	2,6-dichloro	[50]
51	methoxy	2-pyrrolidin-1-ylethoxy	2,6-dichloro	[51]
52	methoxy	2-pyrrolidin-1-ylethoxy	2,6-difluoro	[52]
53	methoxy	2-morpholinoethoxy	2,6-dichloro	[53]
54	methoxy	2-morpholinoethoxy	2,6-difluoro	[54]
55	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-dimethyl	[55]
56	methoxy	3-morpholinopropoxy	2,6-dimethyl	[56]
57	methoxy	3-(4-methylpiperazin-1-yl)propoxy	2,6-dimethyl	[57]
58	methoxy	2-pyrrolidin-1-ylethoxy	2,6-dimethyl	[58]
59	methoxy	2-piperidinoethoxy	2,6-dimethyl	[59]
60	methoxy	2-morpholinoethoxy	2,6-dimethyl	[60]
61	methoxy	2-(2-oxoimidazolidin-1-yl)ethoxy	2,6-dimethyl	[61]
62	methoxy	2-dimethylaminoethoxy	2,6-dimethyl	[62]
63	methoxy	3-pyrrolidin-1-ylpropoxy	4-bromo-2,6-dimethyl	[63]
64	methoxy	3-piperidinopropoxy	4-bromo-2,6-dimethyl	[64]
65	methoxy	3-morpholinopropoxy	4-bromo-2,6-dimethyl	[65]
66	methoxy	3-(4-methylpiperazin-1-yl)propoxy	4-bromo-2,6-dimethyl	[66]
67	methoxy	2-piperidinoethoxy	4-bromo-2,6-dimethyl	[67]

68	methoxy	2-morpholinoethoxy	4-bromo-2,6-dimethyl	[68]
69	methoxy	2-(2-oxoimidazolidin-1-yl)ethoxy	4-bromo-2,6-dimethyl	[69]
70	methoxy	2-(2-methoxyethoxy)ethoxy	2,6-dichloro	[70]
71	methoxy	2-(2-methoxyethoxy)ethoxy	2,6-difluoro	[71]
72	methoxy	2-(2-methoxyethoxy)ethoxy	2,6-dimethyl	[72]
73	methoxy	N-methylpiperidin-4-ylmethoxy	2-fluoro-6-trifluoromethyl	[73]
74	hydrogen	2-pyrrolidin-1-ylethoxy	2,6-dichloro	[74]
75	hydrogen	2-pyrrolidin-1-ylethoxy	2-chloro-6-methyl	[75]
76	hydrogen	2-pyrrolidin-1-ylethoxy	2-chloro	[76]
77	hydrogen	2-pyrrolidin-1-ylethoxy	2,4,6-trichloro	[77]
78	hydrogen	2-piperidinoethoxy	2,6-dichloro	[78]
79	hydrogen	2-piperidinoethoxy	2,6-difluoro	[79]
80	hydrogen	2-piperidinoethoxy	2-chloro-6-methyl	[80]
81	hydrogen	2-piperidinoethoxy	2-chloro	[81]
82	hydrogen	2-piperidinoethoxy	2,4,6-trichloro	[82]
83	hydrogen	2-(4-methylpiperazin-1-yl)ethoxy	2,6-dichloro	[83]
84	hydrogen	2-(4-methylpiperazin-1-yl)ethoxy	2-chloro-6-methyl	[84]
85	hydrogen	2-(4-methylpiperazin-1-yl)ethoxy	2-chloro	[85]
86	hydrogen	2-(4-methylpiperazin-1-yl)ethoxy	2,4,6-trichloro	[86]
87	hydrogen	N-methylpiperidin-3-ylmethoxy	2,6-dichloro	[87]
88	hydrogen	N-methylpiperidin-3-ylmethoxy	2,6-difluoro	[88]
89	hydrogen	N-methylpiperidin-3-ylmethoxy	2-chloro-6-methyl	[89]
90	hydrogen	N-methylpiperidin-3-ylmethoxy	2-chloro	[90]
91	hydrogen	N-methylpiperidin-3-ylmethoxy	2,4,6-trichloro	[91]
92	hydrogen	3-pyrrolidin-1-ylpropoxy	2,6-dichloro	[92]
93	hydrogen	3-pyrrolidin-1-ylpropoxy	2,6-difluoro	[93]
94	hydrogen	3-pyrrolidin-1-ylpropoxy	2-chloro-6-methyl	[94]
95	hydrogen	3-pyrrolidin-1-ylpropoxy	2-chloro	[95]
96	hydrogen	3-pyrrolidin-1-ylpropoxy	2,4,6-trichloro	[96]
97	hydrogen	3-morpholinopropoxy	2,6-difluoro	[97]

98	hydrogen	3-morpholinopropoxy	2-chloro-6-methyl	[98]
99	hydrogen	3-morpholinopropoxy	2,4,6-trichloro	[99]
100	hydrogen	3-(4-methylpiperazin-1-yl)propoxy	2,6-dichloro	[100]
101	hydrogen	3-(4-methylpiperazin-1-yl)propoxy	2-chloro	[101]
102	hydrogen	3-(4-methylpiperazin-1-yl)propoxy	2,4,6-trichloro	[102]
103	hydrogen	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	2,6-difluoro	[103]
104	hydrogen	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	2-chloro-6-methyl	[104]
105	hydrogen	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	2,4,6-trichloro	[105]
106	hydrogen	3-(1,2,3-triazol-1-yl)propoxy	2,4,6-trichloro	[106]
107	hydrogen	(*E*)-4-pyrrolidin-1-ylbut-2-enyloxy	2,6-difluoro	[107]
108	hydrogen	(*E*)-4-pyrrolidin-1-ylbut-2-enyloxy	2-chloro-6-methyl	[108]
109	hydrogen	(*E*)-4-pyrrolidin-1-ylbut-2-enyloxy	2-chloro	[109]
110	methoxy	3-(4-carbamoylpiperidin-1-yl)propoxy	2,6-dichloro	[110]
111	methoxy	3-(4-carbamoylpiperidin-1-yl)propoxy	2,6-difluoro	[111]
112	methoxy	3-(4-carbamoylpiperidin-1-yl)propoxy	2,6-dimethyl	[112]
113	methoxy	3-(4-carbamoylpiperidin-1-yl)propoxy	2-chloro-6-methyl	[113]
114	hydrogen	3-(pyrrolidin-1-yl)-1-propynyl	2,6-dichloro	[114]
115	methoxy	3-(pyrrolidin-1-yl)-1-propynyl	2,6-dichloro	[115]
116	methoxy	6-morpholino-1-hexynyl	2,6-dichloro	[116]
117	methoxy	6-morpholino-1-hexynyl	2,6-difluoro	[117]
118	methoxy	6-(2-methylimidazol-1-yl)-1-hexynyl	2,6-dichloro	[118]
119	methoxy	6-(2-methylimidazol-1-yl)-1-hexynyl	2,6-difluoro	[119]

120	methoxy	3-dimethylamino-1-propynyl	2,6-difluoro	[120]
121	methoxy	N-methylpiperidin-4-ylmethoxy	2-nitro	[121]
122	methoxy	N-methylpiperidin-4-ylmethoxy	2-methyl-3-fluoro	[122]
123	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-dichloro	[123]
124	methoxy	N-methylpiperidin-4-ylmethoxy	2-methyl-5-nitro	[124]
125	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro-5-trifluoromethyl	[125]
126	methoxy	N-methylpiperidin-4-ylmethoxy	5-chloro-2-methoxy	[126]
127	methoxy	N-methylpiperidin-4-ylmethoxy	2-methoxy-5-methyl	[127]
128	methoxy	N-methylpiperidin-4-ylmethoxy	5-chloro-2-methyl	[128]
129	methoxy	N-methylpiperidin-4-ylmethoxy	2-methyl-5-fluoro	[129]
130	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro-5-methyl	[130]
131	methoxy	3-pyrrolidin-1-ylpropoxy	2,5-difluoro	[131]
132	methoxy	3-pyrrolidin-1-ylpropoxy	2,5-dichloro	[132]
133	methoxy	3-pyrrolidin-1-ylpropoxy	5-chloro-2-methyl	[133]
134	methoxy	3-pyrrolidin-1-ylpropoxy	5-fluoro-2-methyl	[134]
135	methoxy	3-pyrrolidin-1-ylpropoxy	2-methyl-5-nitro	[135]
136	methoxy	3-pyrrolidin-1-ylpropoxy	2-chloro-5-methyl	[136]
137	methoxy	6-(N-methylpiperazin-1-yl)-1-hexynyl	2,6-dichloro	[137]
138	methoxy	benzyloxy	3-dimethylcarbamoyl-2,6-dimethyl	[138]
139	methoxy	cyclopropylmethoxy	2,6-dimethyl	[139]
140	methoxy	6-(N-methylpiperazin-1-yl)hexyl	2,6-dichloro	[140]
141	methoxy	3-(pyrrolidin-1-yl)propyl	2,6-dichloro	[141]
142	methoxy	N-[3-(N-methylpiperazin-1-yl)propyl]carbamoyl	2,6-dichloro	[142]
143	methoxy	N-[3-(imidazol-1-yl)propyl]carbamoyl	2,6-dichloro	[143]
144	methoxy	N-methylpiperazin-1-yl	2,6-dichloro	[144]

145	methoxy	N-(tert-butoxycarbonyl)piperazin-1-yl	2,6-dichloro	[145]
146	methoxy	3-morpholinopropylamino	2,6-dichloro	[146]
147	methoxy	3-imidazol-1-ylpropylamino	2,6-dichloro	[147]
148	methoxy	N-methylpiperidin-4-ylmethoxy	3-dimethylcarbamoyl-2,6-dimethyl	[148]
149	methoxy	3-pyrrolidin-1-ylpropoxy	2-chloro-6-methyl	[149]
150	methoxy	3-methoxypropylamino	2,6-dichloro	[150]
151	methoxy	2-aminoethylamino	2,6-dichloro	[151]
152	methoxy	N-(2-diethylaminoethyl)-N-methylamino	2,6-dichloro	[152]

Notes

[1] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.36 (m, 2H), 1.74 (d, 3H), 1.86 (t, 2H), 2.14 (s, 3H), 2.87 (d, 2H), 3.96 (s, 3H), 4.03 (d, 2H), 7.11 (t, 1H), 7.29 (s, 3H), 7.38 (t, 1H), 7.56 (d, 1H), 8.08 (s, 1H), 8.41 (d, 1H), 8.73 (s, 1H), 10.59 (s, 1H), 13.2 (s, 1H); Mass Spectrum: $M+H^+$ 456 and 458.

[2] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.87 (m, 2H), 2.11 (m, 3H), 2.78 (m, 2H), 2.78 (s, 3H), 3.68 (d, 2H), 4.07 (s, 3H), 4.1 (s, 2H), 7.12 (m, 2H), 7.43 (s, 1H), 7.78 (s, 1H), 8.28 (m, 1H), 8.75 (s, 1H), 13.2 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

[3] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.83 (m, 2H), 2.1 (m, 3H), 2.63 (m, 2H), 2.7 (s, 3H), 3.6 (d, 2H), 4.08 (s, 3H), 4.1 (d, 2H), 7.23 (m, 1H), 7.33 (s, 1H), 7.46 (s, 1H), 7.72 (s, 1H), 8.31 (d, 1H), 8.74 (s, 1H), 13.3 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

[4] Methylene chloride was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.34 (q, 2H), 1.74 (d, 3H), 1.86 (t, 2H), 2.15 (s, 3H), 2.78 (d, 2H), 3.96 (s, 3H), 4.02 (d, 2H), 7.08–7.16 (m, 1H), 7.19–7.36 (m, 3H), 8.06 (s, 1H), 8.27 (s, 1H), 8.69 (s, 1H), 10.56 (s, 1H), 12.81 (s, 1H); Mass Spectrum: $M+H^+$ 440.

[5] DMF was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.35 (m, 2H), 1.8 (m, 5H), 2.15 (s, 3H), 2.79 (d, 2H), 2.94 (s, 3H), 4.03 (d, 2H), 7.1-7.35 (m, 5H), 8.03 (s, 1H), 8.66 (s, 1H), 10.6 (s, 1H); Mass Spectrum: $M+H^+$ 458.

[6] DMF was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H), 1.7-1.8 (m, 4H), 1.85 (t, 1H), 2.2 (s, 3H), 2.8 (d, 2H), 3.9 (s, 3H), 4.1 (br d, 2H), 7.0 (t, 1H), 7.3 (br s, 1H), 7.4 (t, 1H), 7.7 (d, 1H), 8.1 (br s, 1H), 8.4 (d, 1H), 8.8 (s, 1H), 10.5 (br s, 1H); Mass Spectrum: $M+H^+$ 500 and 502.

[7] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.97 (m, 5H), 2.3 (s, 3H), 2.88 (d, 2H), 3.61 (s, 3H), 4.01 (d, 2H), 7.24 (s, partially obscured by $CHCl_3$ peak), 7.25 (t, partially obscured by $CHCl_3$ peak), 7.37 (s, 1H), 7.56 (t, 1H), 7.7 (d, 1H), 8.17 (d, 1H), 8.7 (s, 1H), 9.36 (s, 1H), 13.2 (s, 1H); Mass Spectrum: $M+H^+$ 490.

[8] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.38–1.55 (m, 2H), 1.84–2.04 (m, 5H), 2.3 (s, 3H), 2.47 (s, 3H), 2.91 (d, 2H), 3.66 (s, 3H), 4.01 (d, 2H), 7.05–7.14 (m, 1H), 7.17–7.28 (m, 4H), 7.4 (s, 1H), 7.96 (d, 1H), 8.7 (s, 1H), 9.24 (s, 1H), 12.34 (s, 1H); Mass Spectrum: $M+H^+$ 436.

[9] The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CD_3COOH) 1.5–1.67 (q, 2H), 1.93–2.17 (m, 3H), 2.24 (s, 6H), 2.71 (s, 3H), 2.93 (t, 2H), 3.37 (d, 2H), 3.95 (s, 3H), 4.09 (d, 2H), 7.1 (s, 3H), 7.31 (s, 1H), 8.07 (s, 1H), 8.66 (d, 1H); Mass Spectrum: $M+H^+$ 450.

[10] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.43 (m, 2H), 1.5 (s, 9H), 1.82 (m, 5H), 2.28 (s, 3H), 2.89 (d, 2H), 3.32 (s, 3H), 4.0 (d, 2H), 7.2 (m, 3H), 7.5 (m, 2H), 7.57 (s, 1H), 8.62 (s, 1H), 9.9 (s, 1H), 12.35 (s, 1H); Mass Spectrum: $M+H^+$ 478.

[11] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.45 (m, 2H), 1.59 (m, 4H), 2.11 (m, 2H), 2.33 (s, 6H), 2.4 (br s, 4H), 2.5 (t, 2H), 3.23 (s, 3H), 4.22 (t, 2H), 7.14 (m, 3H), 7.28 (s, 1H), 7.62 (s, 1H), 8.66 (s, 1H), 10.16 (s, 1H), 12.08 (s, 1H); Mass Spectrum: $M+H^+$ 513.

The 4-amino-6-methoxy-7-(3-piperidinopropoxy)quinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml). The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with

brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: ($DMSOd_6$) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); NMR Spectrum: ($DMSOd_6$) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

Diethyl azodicarboxylate (3.9 ml) was added dropwise to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (5 g), 3-bromopropanol (2.21 ml), triphenylphosphine (6.42 g) and methylene chloride (50 ml) and the mixture was stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(3-bromopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6 g); NMR Spectrum: ($DMSOd_6$) 1.12 (s, 9H), 2.32 (t, 2H), 3.7 (t, 2H), 3.9 (s, 3H), 4.25 (t, 2H), 5.9 (s, 2H), 7.20 (s, 1H), 7.61 (s, 1H), 8.36 (s, 1H).

A mixture of a portion (2.89 g) of the material so obtained and piperidine (10 ml) was stirred and heated to 100°C for 1 hour. The mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-methoxy-7-(3-piperidinopropoxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2.4 g); NMR Spectrum: ($DMSOd_6$) 1.15 (s, 9H), 1.35-1.5 (m, 1H), 1.6-1.8 (m, 3H), 1.8-1.9 (d, 2H), 2.2-2.3 (m, 2H), 2.95 (t, 2H), 3.25 (t, 2H), 3.55 (d, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 5.94 (s, 2H), 7.24 (s, 1H), 7.56 (s, 1H), 8.36 (s, 1H).

A mixture of the material so obtained and a 7N solution of ammonia in methanol (50 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the

residue was triturated under diethyl ether. The resultant solid was isolated, washed in turn with diethyl ether and a 1:1 mixture of diethyl ether and methylene chloride and dried under vacuum. There was thus obtained 6-methoxy-7-(3-piperidinopropoxy)-3,4-dihydroquinazolin-4-one (1.65 g); NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.4-1.55 (m, 4H), 1.85-1.95 (m, 2H), 2.35 (br s, 4H), 2.4 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.9 (s, 1H).

A mixture of the material so obtained, thionyl chloride (15 ml) and DMF (1.5 ml) was heated to reflux for 3 hours. The mixture was evaporated. Toluene was added and the mixture was again evaporated. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution (the basicity of which was adjusted to pH10 by adding 6N aqueous sodium hydroxide). The organic layer was separated, washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (1.2 g); NMR Spectrum: ($DMSOd_6$) 1.35-1.45 (m, 2H), 1.5-1.6 (m, 4H), 1.9-2.05 (m, 2H), 2.4 (br s, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.29 (t, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

A portion (0.5 g) of the material so obtained was dissolved in a 1M solution of ammonia in isopropanol (10 ml). Liquid ammonia (1 ml) was added and the reaction mixture was sealed in a Carius tube. The reaction mixture was heated to 120°C for 16 hours. The Carius tube was cooled and opened and the reaction mixture was evaporated. The residue was stirred under a 2N aqueous sodium hydroxide solution for 1 hour. The resultant solid was isolated and washed in turn with water and methyl tert-butyl ether. There was thus obtained 4-amino-6-methoxy-7-(3-piperidinopropoxy)quinazoline (0.225 g); NMR Spectrum: ($DMSOd_6$) 1.37 (d, 2H), 1.49 (t, 4H), 1.91 (m, 2H), 2.3 (s, 4H), 2.37 (t, 2H), 3.86 (s, 3H), 4.1 (t, 2H), 7.04 (s, 1H), 7.38 (s, 2H), 7.54 (s, 1H), 8.22 (s, 1H); Mass Spectrum: $M+H^+$ 317.

[12] Acetonitrile was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.5 (br s, 4H), 2.7 (t, 2H), 3.75 (t, 4H), 4.25 (t, 2H), 7.15 (d, 1H), 7.3 (m, 2H), 7.5 (d, 2H), 8.1 (d, 1H), 8.85 (s, 1H), 9.05 (s, 1H), 12.1 (s, 1H); Mass Spectrum: $M+H^+$ 476 and 478.

The 4-amino-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

A solution of 2-amino-4-fluorobenzoic acid (3 g) in formamide (30 ml) was heated to 150°C for 6 hours. The reaction mixture was poured onto a 1:1 mixture of ice and water

(250 ml) and the precipitated solid was collected, washed with water and dried to give 7-fluoro-3,4-dihydroquinazolin-4-one (2.6 g).

Sodium metal (4.4 g) was added to benzyl alcohol (100 ml) and the resultant mixture was stirred at ambient temperature for 30 minutes and then and heated to 80°C for 1 hour. The mixture was cooled to 40°C and 7-fluoro-3,4-dihydroquinazolin-4-one (7.8 g) was added. The reaction mixture was stirred and heated to 130°C for 4 hours. The mixture was allowed to cool to ambient temperature and was stirred for a further 18 hours. The solution was quenched with water (800 ml) and acidified to pH3 by the addition of concentrated hydrochloric acid. The resultant precipitate was collected, washed in turn with water and diethyl ether and dried under vacuum for 4 hours at 60°C. There was thus obtained 7-benzyloxy-3,4-dihydroquinazolin-4-one (7.02 g).

A mixture of the material so obtained, phosphorus pentasulphide (12.5 g) and pyridine (350 ml) was stirred and heated to reflux for 8 hours. After cooling, the mixture was poured into water (1 L). The precipitate was collected and washed with water. The solid so obtained was dissolved in 6N aqueous sodium hydroxide solution and the solution was filtered. The filtrate was acidified to pH2 by the addition of 6N aqueous hydrochloric acid. The resultant precipitate was collected, washed with water and dried under vacuum at 60°C. There was thus obtained 7-benzyloxy-3,4-dihydroquinazolin-4-thione (7.42 g); NMR Spectrum: ($DMSOd_6$) 5.32 (s, 2H), 7.25 (d, 1H), 7.32 (m, 1H), 7.4 (m, 1H), 7.45 (t, 2H), 7.55 (d, 2H), 8.15 (s, 1H), 8.5 (d, 1H).

A portion (3.45 g) of the material so obtained was dissolved in THF (13 ml) and 1N aqueous sodium hydroxide solution (25.7 ml) was added. Methyl iodide (0.97 ml) was added dropwise and the mixture was stirred at ambient temperature for 30 minutes. The mixture was neutralised by the addition of 2N aqueous hydrochloric acid and the mixture was diluted by the addition of water. The resultant solid was collected, washed with water and dried under vacuum to give 7-benzyloxy-4-methylthioquinazoline (3.3 g); NMR Spectrum: ($DMSOd_6$) 2.67 (s, 3H), 5.32 (s, 2H), 7.3-7.45 (m, 5H), 7.5 (d, 2H), 8.05 (d, 1H), 8.9 (s, 1H).

A mixture of a portion (3 g) of the material so obtained and trifluoroacetic acid (30 ml) was heated to reflux for 5 hours. The mixture was evaporated. The residue was suspended in water and solid sodium bicarbonate was added until complete dissolution. The solution was extracted with diethyl ether. The aqueous layer was acidified to pH2 by the addition of 2N aqueous hydrochloric acid and the resultant precipitate was collected, washed in turn with water and diethyl ether and dried under vacuum. There was thus obtained 7-hydroxy-

4-methylthioquinazoline (2 g); NMR Spectrum: ($DMSOd_6$) 2.7 (s, 3H), 7.15 (d, 1H), 7.25 (m, 1H), 8.0 (d, 1H), 8.9 (s, 1H).

Diethyl azodicarboxylate (2.92 g) was added dropwise to a stirred mixture of 7-hydroxy-4-methylthioquinazoline (2.5 g), 4-(3-hydroxypropyl)morpholine (Bull. Soc. Chim. Fr. 1962, 1117; 2.47 g), triphenylphosphine (4.45 g) and methylene chloride (65 ml). The reaction mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was partitioned between a 1:1 mixture of ethyl acetate and diethyl ether and a 1N aqueous hydrochloric acid solution. The aqueous layer was separated, basified to pH9 by the addition of solid sodium bicarbonate and extracted with methylene chloride. The organic layer was separated, washed with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, ethyl acetate and methanol (from 6:3:1 to 5:3:2 to 75:0:25) as eluent. There was thus obtained 4-methylthio-7-(3-morpholinopropoxy)-quinazoline (2.03 g); NMR Spectrum: ($DMSOd_6$,and CF_3COOD) 2.2-2.3 (m, 2H), 2.7 (s, 3H), 3.05-3.25 (m, 2H), 3.35 (t, 2H), 3.55 (d, 2H), 3.7 (t, 2H), 4.05 (d, 2H), 4.32 (t, 2H), 7.38 (d, 1H), 7.4 (s, 1H), 8.1 (d, 1H), 9.05 (d, 1H); Mass Spectrum : $M+H^+$ 320.

A mixture of a portion (0.5 g) of the material so obtained and a solution of ammonia gas in methanol (7M; 50 ml) was sealed in a pressure vessel and heated to 120°C for 16 hours. The mixture was cooled to ambient temperature and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, methanol and a 1% aqueous ammonium hydroxide solution as eluent. The material so obtained was triturated under diethyl ether and the resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 4-amino-7-(3-morpholinopropoxy)quinazoline (0.35 g); NMR Spectrum: ($CDCl_3$) 2.0-2.15 (m, 2H), 2.5 (br s, 4H), 2.6 (t, 2H), 3.75 (br s, 4H), 4.2 (t, 2H), 5.65 (br s, 2H), 7.1 (d, 1H), 7.2 (s, 1H), 7.65 (d, 1H), 8.55 (s, 1H) ; Mass Spectrum : $M+H^+$ 280.

[13] Acetonitrile was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.05 (m, 2H), 2.75 (t, 2H), 3.0-3.15 (m, 8H), 4.2 (t, 2H), 7.1 (d, 1H), 7.2-7.35 (m, 2H), 7.5 (d, 2H), 8.2 (d, 1H), 8.8 (s, 1H), 9.45 (s, 1H); Mass Spectrum: $M+H^+$ 524 and 526; Elemental Analysis: Found C, 50.0; H, 4.4; N, 13.3; $C_{22}H_{23}N_5O_4Cl_2S$ requires C, 50.39; H, 4.42; N, 13.35%.

The 4-amino-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline used as a starting material was prepared as follows :-

A mixture of 3-aminopropan-1-ol (0.650 ml) and divinyl sulphone (1 g) was heated to 110°C for 45 minutes. The mixture was allowed to cool to ambient temperature and was purified by column chromatography on silica usin a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol (0.8 g); NMR Spectrum: ($CDCl_3$) 1.7-1.8 (m, 2H), 2.73 (t, 2H), 3.06 (br s, 8H), 3.25 (s, 1H), 3.78 (t, 2H); Mass Spectrum: $M+H^+$ 194.

Diethyl azodicarboxylate (3.3 ml) was added dropwise to a stirred mixture of 7-hydroxy-4-methylthioquinazoline (1.34 g), 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol (2.03 g), triphenylphosphine (5.51 g) and methylene chloride (100 ml). The reaction mixture was stirred at ambient temperature for 4 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using initially ethyl acetate and then a 24:1 mixture of ethyl acetate and ethanol as eluent. There was thus obtained 7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-4-methylthioquinazoline (1.79 g); NMR Spectrum: ($CDCl_3$) 2.05 (m, 2H), 2.7 (s, 3H), 2.73 (t, 2H), 3.05 (m, 8H), 4.2 (t, 2H), 7.15 (m, 1H), 7.2 (d, 1H), 8.0 (d, 1H), 8-9 (s, 1H); Mass Spectrum: $M+H^+$ 368.

Using an analogous procedure to that described in the last paragraph of Note [12] immediately above, a portion (0.5 g) of the material so obtained was reacted with ammonia gas in methanol. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of chloroform and methanol as eluent. There was thus obtained 4-amino-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline (0.45 g); NMR Spectrum ($CDCl_3$) 2.05 (m, 2H), 2.75 (t, 2H), 3.0-3.1 (m, 8H), 4.2 (t, 2H), 5.5 (br s, 2H), 7.15 (m, 1H), 7.2 (s, 1H), 7.65 (d, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 337.

[14] Acetonitrile was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 3.0-3.4 (m, 2H), 3.4 (br d, 2H), 3.6-3.7 (m, 2H), 3.95 (br d, 2H), 4.25 (s, 2H), 5.2 (s, 2H), 7.32 (t, 1H), 7.5 (d, 2H), 7.5-7.6 (m, 2H), 8.9 (d, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 486 and 488; Elemental Analysis: Found C, 55.4; H, 4.3; N, 14.1; $C_{23}H_{21}N_5O_3Cl_2$ 0.6 H_2O requires C, 55.57; H, 4.50; N, 14.09 %.

The 4-amino-7-(4-morpholinobut-2-yn-1-yloxy)quinazoline used as a starting material was prepared as follows :-

Diethyl azodicarboxylate (2.46 ml) was added dropwise to a stirred mixture of 7-hydroxy-4-methylthioquinazoline (1.2 g), 4-morpholinobut-2-yn-1-ol (J. Amer. Chem. Soc., 1957, 79, 6184; 1.26 g), triphenylphosphine (4.09 g) and methylene chloride (35 ml). The reaction mixture was stirred at ambient temperature for 3 hours. The mixture was evaporated

and the residue was purified by column chromatography on silica using initially methylene chloride and then a 19:1 mixture of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether. The resultant solid was collected and dried under vacuum. There was thus obtained 4-methylthio-7-(4-morpholinobut-2-yn-1-yloxy)quinazoline (1.3 g); NMR Spectrum: ($CDCl_3$) 2.5 (t, 4H), 2.7 (s, 3H), 3.32 (t, 2H), 3.7 (t, 4H), 4.9 (t, 2H), 7.2 (d, 1H), 7.35 (d, 1H), 8.0 (d, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 330.

Using an analogous procedure to that described in the last paragraph of Note [12] above, a portion (0.5 g) of the material so obtained was reacted with a saturated solution of ammonia gas in methanol. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, methanol and a 1% aqueous ammonium hydroxide solution as eluent. There was thus obtained 4-amino-7-(4-morpholinobut-2-yn-1-yloxy)quinazoline (0.283 g); NMR Spectrum: ($DMSOd_6$) 2.4 (m, 4H), 3.3 (t, 2H), 3.5 (m, 4H), 5.0 (s, 2H), 7.15 (m, 1H), 7.18 (d, 1H), 7.6 (br s, 2H), 8.15 (d, 1H), 8.32 (s, 1H); Mass Spectrum: $M+Na^+$ 321; Elemental Analysis: Found C, 63.8; H, 6.1; N, 18.7; $C_{16}H_{18}N_4O_2$ 0.2 H_2O requires C, 63.65; H, 6.14; N, 18.55 %.

[15] Acetonitrile was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 3.0-3.1 (m, 2H), 3.4 (d, 2H), 3.65 (t, 2H), 3.85 (d, 2H), 4.0 (d, 2H), 4.95 (br s, 2H), 6.0 (m, 1H), 6.3 (m, 1H), 7.4 (t, 1H), 7.45 (s, 1H), 7.55 (m, 1H), 7.6 (d, 2H), 8.85 (d, 1H), 9.17 (s, 1H); Mass Spectrum: $M+Na^+$ 510 and 512; Elemental Analysis: Found C, 56.2; H, 4.7; N, 14.2; $C_{23}H_{23}N_5O_3Cl_2$ requires C, 56.57; H, 4.75; N, 14.34 %.

The 4-amino-7-[(*E*)-4-morpholinobut-2-en-1-yloxy]quinazoline used as a starting material was prepared as follows :-

Using an analogous procedure to that described in the second last paragraph of Note [12] above, (*E*)-4-morpholinobut-2-en-1-ol (J. Med. Chem., 1972, 15, 110-112; 1.27 g), was reacted with 7-hydroxy-4-methylthioquinazoline (1.2 g) to give 4-methylthio-7-[(*E*)-4-morpholinobut-2-en-1-yloxy]quinazoline (1.15 g); NMR Spectrum: ($CDCl_3$) 2.45 (br s, 4H), 2.7 (s, 3H), 3.05 (d, 2H), 3.7 (t, 4H), 4.7 (d, 2H), 5.9 (m, 2H), 7.15-7.25 (m, 2H), 7.95 (d, 1H), 8.9 (d, 1H); Mass Spectrum: $M+H^+$ 332.

Using an analogous procedure to that described in the last paragraph of Note [12] above, 4-methylthio-7-[(*E*)-4-morpholinobut-2-en-1-yloxy]quinazoline (0.5 g) was reacted with a saturated solution of ammonia gas in methanol. The reaction product was purified by

column chromatography on silica using increasingly polar mixtures of methylene chloride, methanol and a 1% aqueous ammonium hydroxide solution as eluent. There was thus obtained 4-amino-7-[(*E*)-4-morpholinobut-2-en-1-yloxy]quinazoline (0.372 g); NMR Spectrum: ($DMSOd_6$) 2.35 (br s, 4H), 3.0 (br s, 2H), 3.56 (t, 4H), 4.7 (br s, 2H), 5.9 (br s, 2H), 7.05 (s, 2H), 7.1 (m, 1H), 7.6 (br s, 2H), 8.12 (d, 1H), 8.3 (s, 1H); Mass Spectrum : $M+Na^+$ 323; Elemental Analysis: Found C, 63.1; H, 6.7; N, 18.4; $C_{16}H_{20}N_4O_2$ 0.2 H_2O requires C, 63.22; H, 6.76; N, 18.51 %.

[16] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.4 (m, 1H), 1.7 (m, 3H), 1.9 (m, 2H), 3.1 (t, 2H), 3.65 (m, 4H), 4.05 (s, 3H), 4.65 (t, 2H), 7.45 (t, 1H), 7.52 (s, 1H), 7.62 (d, 2H), 8.3 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

The 4-amino-6-methoxy-7-(2-piperidinoethoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (25.1 g), thionyl chloride (450 ml) and DMF (1 ml) was stirred and heated to reflux for 2 hours. The mixture was evaporated and the residue was dissolved in toluene and the solution was evaporated. The resultant solid was suspended in methylene chloride (500 ml), solid potassium carbonate (39 g) was added and the mixture was stirred for 10 minutes. Water (500 ml) was added and the mixture stirred for another 10 minutes. The methylene chloride layer was separated, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 7-benzyloxy-4-chloro-6-methoxyquinazoline (21.54 g); NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H), 5.36 (s, 2H), 7.31–7.46 (m, 4H), 7.51 (d, 2H), 7.58 (s, 1H), 8.88 (s, 1H).

A portion (3 g) of the material so obtained was dissolved in a 1M solution of ammonia in isopropanol (50 ml). Liquid ammonia (5 ml) was added and the reaction mixture was sealed in a Carius tube. The reaction mixture was heated to 120°C for 16 hours. The Carius tube was cooled and opened and the reaction mixture was evaporated. The residue was stirred under a 2N aqueous sodium hydroxide solution for 1 hour. The resultant solid was isolated and washed in turn with water and methyl tert-butyl ether. There was thus obtained 4-amino-

7-benzyloxy-6-methoxyquinazoline (2.65 g); NMR Spectrum: ($DMSOd_6$) 3.88 (s, 3H), 3.9 (s, 3H), 7.2 (s, 1H), 7.63 (s, 2H), 7.69 (s, 1H), 8.38 (s, 1H); Mass Spectrum: $M+H^+$ 230.

A mixture of 4-amino-7-benzyloxy-6-methoxyquinazoline (4.15 g) and trifluoroacetic acid (35 ml) was stirred and heated to reflux for 1 hour. The solvent was evaporated, the residue was redissolved in a mixture of methylene chloride and toluene and the solvent was evaporated. The solid so obtained was suspended in water and basified to pH11 by the addition of 2N aqueous sodium hydroxide solution. The mixture was then neutralised to pH7 by the addition of 1N aqueous hydrochloric acid solution. The resultant solid was collected, washed in turn with water and acetonitrile and dried under vacuum over phosphorus pentoxide. There was thus obtained 4-amino-7-hydroxy-6-methoxyquinazoline (2.55 g); NMR Spectrum: ($DMSOd_6$) 3.9 (s, 3H), 7.05 (s, 1H), 7.65 (s, 1H), 8.0 (br s, 2H), 8.35 (s, 1H), 10.0-11.0 (br s, 1H).

A portion (0.15 g) of the material so obtained and triphenylphosphine (0.31 g) were dissolved in DMF (3 ml). THF (3 ml) was added causing partial precipitation of the starting material. A solution of N-(2-hydroxyethyl)piperidine (0.111 g) in THF (1 ml) was added followed by diethyl azodicarboxylate (0.186 ml) and the reaction mixture was stirred at ambient temperature for 30 minutes. Further portions of triphenylphosphine (0.105 g), N-(2-hydroxyethyl)piperidine (0.02 g) and diethyl azodicarboxylate (0.062 ml) were added and reaction mixture was stirred at ambient temperature for a further 30 minutes. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the required starting material (0.18 g); NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.4 (m, 1H), 1.7 (m, 3H), 1.8 (m, 2H), 3.15 (m, 2H), 3.65 (m, 4H), 3.95 (s, 3H), 4.55 (t, 2H), 7.3 (s, 1H), 7.9 (s, 1H), 8.75 (s, 1H), 9.45 (br s, 1H); Mass Spectrum: $M+H^+$ 303.

[17] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 2.3 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (m, 2H), 3.7 (t, 2H), 4.0 (s, 3H), 4.05 (m, 2H), 4.35 (t, 2H), 7.45 (t, 1H), 7.63 (d, 2H), 8.25 (s, 1H), 8.3 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 506 and 508.

The 4-amino-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and N-(3-hydroxypropyl)morpholine using an analogous procedure to that described in the last

paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: (DMSOd_6 and CF_3COOD) 2.25 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (m, 2H), 3.7 (t, 2H), 3.95 (s,3H), 4.05 (m, 2H), 4.3 (t, 2H), 7.35 (s, 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.4 (br s, 1H); Mass Spectrum: $M+H^+$ 319.

[18] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: (DMSOd_6, and CF_3COOD) 2.3 (m, 2H), 2.95 (s, 3H), 3.2-3.8 (br s, 8H), 3.45 (m, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.45 (t, 1H), 7.47 (s, 1H), 7.62 (d, 2H), 8.3 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 519 and 521.

The 4-amino-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and 1-(3-hydroxypropyl)-4-methylpiperazine using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: (DMSOd_6 and CF_3COOD) 2.3 (m, 2H), 2.95 (s, 3H), 3.2-3.8 (br s, 8H), 3.4 (m, 2H), 3.95 (s, 3H), 4.3 (t, 2H), 7.25 (s, 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.4 (br s, 1H); Mass Spectrum: $M+H^+$ 332.

[19] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: (DMSOd_6, and CF_3COOD) 1.9 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 3.1 (m, 2H), 3.35 (m, 2H), 3.65 (m, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.45 (t, 1H), 7.47 (s, 1H), 7.63 (d, 2H), 8.3 (s, 1H), 9.1 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

The 4-amino-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and N-(3-hydroxypropyl)pyrrolidine using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: (DMSOd_6 and CF_3COOD) 1.9 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 3.05 (m, 2H), 3.35 (m, 2H), 3.65 (m, 2H), 3.95 (s, 3H), 4.3 (t, 2H), 7.25 (s, 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.4 (br s, 1H); Mass Spectrum: $M+H^+$ 303.

[20] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following

data: NMR Spectrum: ($DMSOd_6$, and CF_3COOD) 2.3 (m, 2H), 3.5 (t, 2H), 3.65 (m, 4H), 3.85 (m, 4H), 4.05 (s, 3H), 4.35 (t, 2H), 7.43 (t, 1H), 7.46 (s, 1H), 7.65 (d, 2H), 8.3 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 554 and 556.

The 4-amino-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and N-(3-hydroxypropyl)-1,1-dioxotetrahydro-4H-1,4-thiazine using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 2.3 (m, 2H), 3.5 (m, 2H), 3.65 (m, 4H), 3.85 (m, 4H), 3.95 (s, 3H), 4.25 (t, 2H), 7.25 (s, 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.4 (br s, 1H); Mass Spectrum: $M+H^+$ 367.

[21] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: ($DMSOd_6$, and CF_3COOD) 2.95 (s, 3H), 3.35 (s, 3H), 3.4 (m , 1H), 3.55 (m , 1H), 3.75 (m, 4H), 4.05 (s, 3H), 4.65 (t, 2H), 7.45 (t, 1H), 7.50 (s, 1H), 7.65 (d, 2H), 8.3 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 494 and 496.

The 4-amino-6-methoxy-7-{2-[N-(2-methoxyethyl)-N-methylamino]ethoxy}-quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and 2-[N-(2-methoxyethyl)-N-methylamino]ethanol using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 2.95 (s, 3H), 3.35 (s, 3H), 3.4 (m , 1H), 3.55 (m , 1H), 3.75 (br m, 4H), 3.95 (s, 3H), 4.55 (t, 2H), 7.25 (s, 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.45 (br s, 1H); Mass Spectrum: $M+H^+$ 307.

The 2-[N-(2-methoxyethyl)-N-methylamino]ethanol used as a starting material was prepared as follows :-

A mixture of 2-methylaminoethanol (5.4 g), 2-bromoethyl methyl ether (10 g), triethylamine (10 ml) and acetonitrile (70 ml) was stirred and heated to reflux for 16 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The organic solution was separated and evaporated to give 2-[N-(2-methoxyethyl)-N-methylamino]ethanol (3 g, 31%); NMR Spectrum: ($CDCl_3$) 2.35 (s, 3H), 2.6 (t, 2H), 2.65 (t, 2H), 3.35 (s, 3H), 3.5 (t, 2H), 3.6 (t, 2H).

[22] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: ($DMSOd_6$, and CF_3COOD) 2.3 (m, 2H), 3.05 (s, 3H), 3.35 (t, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 7.45 (m, 2H), 7.65 (d, 2H), 8.29 (s, 1H), 9.1 (s, 1H); Mass Spectrum: $M+H^+$ 499 and 501.

The 4-amino-6-methoxy-7-(3-mesylpropoxy)quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and 3-mesylpropanol using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 2.3 (m, 2H), 3.05 (s, 3H), 3.3 (t, 2H), 3.95 (s, 3H), 4.3 (t, 2H), 7.2 (s, 1H), 7.85 (s, 1H), 8.75 (s, 1H), 9.45 (br s, 1H); Mass Spectrum: $M+H^+$ 312.

The 3-mesylpropanol used as a starting material was prepared as follows :-

3-Chloroperoxybenzoic acid (25 g) was added in portions to a solution of 3-methylthiopropanol (5 ml) in methylene chloride (100 ml) while maintaining the reaction temperature at 25°C. The mixture was stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate was diluted with an aqueous solution of sodium sulphite (6.5 g) in water (200 ml). The organic layer was separated and evaporated. The white residue was triturated under acetone and the resultant solution was evaporated to give a solid which was dissolved in methylene chloride. Aluminum oxide (90Å mesh) was added and the mixture was allowed to stand for 15 minutes. The mixture was filtered and the filtrate was evaporated to give 3-mesylpropanol as a colourless oil (4.46 g); NMR Spectrum: ($CDCl_3$) 1.9-2.1 (br s, 1H), 2.15 (m, 2H), 2.95 (s, 3H), 3.2 (t, 2H), 3.85 (t, 2H).

[23] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: ($DMSOd_6$, and CF_3COOD) 2.45 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 4.6 (t, 2H), 7.38 (s, 1H), 7.43 (t, 1H), 7.63 (d, 2H), 7.77 (s, 1H), 8.22 (s, 1H), 8.26 (s, 1H), 9.03 (s, 1H); Mass Spectrum: $M+H^+$ 488 and 490.

The 4-amino-6-methoxy-7-[3-(1,2,3-triazol-1-yl)propoxy]quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and N^1-(3-hydroxypropyl)-1,2,3-triazole (see Note [106] hereinafter) using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained

the required starting material; NMR Spectrum: (DMSOd_6 and CF_3COOD) 2.4 (m, 2H), 3.95 (s, 3H), 4.15 (t, 2H), 4.6 (t, 2H), 7.15 (s, 1H), 7.75 (s, 1H), 7.85 (s, 1H), 8.2 (s, 1H), 8.75 (s, 1H), 9.45 (br s, 1H); Mass Spectrum: M+H^+ 301.

[24] Acetonitrile was used as the reaction solvent and the reaction mixture was heated to 35°C for 7 hours and then to 50°C for 5 hours. The resultant precipitate was collected, washed in turn with acetonitrile and diethyl ether and dried. The product gave the following data: NMR Spectrum: (DMSOd_6, and CF_3COOD) 3.55 (t, 2H), 4.0 (s, 3H), 4.65 (t, 2H), 7.45 (t, 1H), 7.5 (s, 1H), 7.65 (d, 2H), 8.15 (d, 2H), 8.3 (s, 1H), 8.95 (d, 2H), 9.1 (s, 1H); Mass Spectrum: M+H^+ 484 and 486.

The 4-amino-6-methoxy-7-[2-(4-pyridyl)ethoxy]quinazoline used as a starting material was prepared by the reaction of 4-amino-7-hydroxy-6-methoxyquinazoline and 4-(2-hydroxyethyl)pyridine (Zhur. Obshchei. Khim., 1958, 28, 103-110) using an analogous procedure to that described in the last paragraph of Note [16] above. There was thus obtained the required starting material; NMR Spectrum: (DMSOd_6 and CF_3COOD) 3.5 (t, 2H), 3.9 (s, 3H), 4.6 (t, 2H), 7.3 (s, 1H), 7.85 (s, 1H), 8.15 (d, 2H), 8.75 (s, 1H), 8.95 (d, 2H), 9.4 (br s, 1H); Mass Spectrum: M+H^+ 297.

[25] The product gave the following data: NMR Spectrum: ($CDCl_3$ + CD_3CO_2D) 1.78–1.9 (m, 2H), 2.05–2.3 (m, 3H), 2.64 (t, 2H), 2.7 (s, 3H), 3.59 (d, 2H), 4.04 (s, 3H), 4.1 (d, 2H), 7.25 (s, 1H), 7.44 (s, 2H), 7.74 (s, 1H), 8.2-8.6 (m, partially obscured by CD_3CO_2H), 8.71 (s, 1H), 12.4 (s, 1H); Mass Spectrum: M+H^+ 524 and 526.

[26] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.41–1.56 (m, 2H), 1.85–2.05 (m, 5H), 2.3 (s, 3H), 2.91 (d, 2H), 3.96 (s, 3H), 4.03 (d, 2H), 6.74 (m, 1H), 7.1 (m, 1H), 7.18 (s, 1H), 7.28 (s, 1H), 8.11 (m, 1H), 8.46 (s, 1H), 8.88 (s, 1H), 12.86 (s, 1H); Mass Spectrum: M+H^+ 458.

[27] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42–1.58 (m, 2H), 1.87–2.08 (m, 5H), 2.31 (s, 3H), 2.93 (d, 2H), 3.84 (s, 3H), 4.02 (d, 2H), 6.9 (m, 2H), 7.28 (m, 2H), 8.16 (m, 1H), 8.76 (s, 1H), 8.86 (s, 1H), 12.65 (s, 1H); Mass Spectrum: M+H^+ 458.

[28] Methylene chloride was used as the reaction solvent. The product was obtained as a 1:1 adduct with DMF and gave the following data: NMR Spectrum: ($CDCl_3$) 1.4-1.55 (m, 2H), 1.9-2.1 (m, 5H), 2.3 (s, 3H), 2.88 (s, 3H), 2.93 (s, 3H), 2.9 (m, partially obscured by DMF signal), 3.72 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.01 (d, 2H), 6.6 (m, 1H) 6.86 (d, 1H), 7.28 (s, 1H), 7.36 (s, 1H), 7.98 (d, 1H), 8.02 (s, 1H), 8.55 (s, 1H), 8.87 (s, 1H), 12.75 (s, 1H); Mass Spectrum: M+H^+ 482 (relating to the parent ion).

[29] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4–1.55 (m, 2H), 1.85–2.1 (m, 5H), 2.29 (s, 3H), 2.9 (d, 2H), 3.8 (s, 3H), 3.82 (s, 3H), 3,96 (s, 3H), 4.03 (d, 2H), 6.48 (m, 1H), 6.56 (d, 1H), 7.25 (s, 1H), 7.38 (s, 1H), 8.08 (d, 1H), 8.72 (s, 1H), 9.07 (s, 1H), 12.4 (s, 1H); Mass Spectrum: $M+H^+$ 482.

[30] Methylene chloride was used as the reaction solvent . The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.17 (br s, 12H), 1.4-1.6 (m, 2H), 1.7 (br s, 2H), 1.85-2.1 (m, 5H), 2.3 (s, 3H), 2.91 (d, 2H), 3.3 (s, 3H), 4.01 (d, 2H), 7.2-7.22 (m, 3H) 7.3-7.4 (m, 1H), 7.5 (s, 1H), 8.62 (s, 1H), 9.7 (s, 1H), 11.4 (s, 1H); Mass Spectrum: $M+H^+$ 506.

[31] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4–1.55 (m, 2H), 1.85–2.1 (m, 5H), 2.28 (s, 6H), 2.3 (s, 3H), 2.34 (s, 3H), 2.9 (d, 2H), 3,37 (s, 3H), 4.01 (d, 2H), 6.91 (s, 2H), 7.22 (s, 1H), 7.3 (s, 1H), 8.64 (s, 1H), 8.7 (s, 1H), 11.8 (s, 1H); Mass Spectrum: $M+H^+$ 464.

[32] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.44–1.59 (m, 2H), 1.86–2.08 (m, 5H), 2.32 (d, 6H), 2.41 (s, 3H), 2.94 (d, 2H), 3.68 (s, 3H), 4.02 (d, 2H), 6.92 (d, 1H), 7.14 (d, 1H), 7.26 (m, 1H), 7.46 (s, 1H), 7.77 (s, 1H), 8.69 (s, 1H), 9.31 (s, 1H), 12.27 (s, 1H); Mass Spectrum: $M+H^+$ 450.

[33] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.18 (t, 6H), 1.4–1.55 (m, 2H), 1.85–2.06 (m, 5H), 2.3 (s, 3H),2.69 (q, 4H) 2.9 (d, 2H), 3.3 (s, 3H), 4.03 (d, 2H), 7.1-7.3 (m, 4H), 7.51 (s, 1H), 8.63 (s, 1H), 9.73 (s, 1H), 11.87 (s, 1H); Mass Spectrum: $M+H^+$ 478.

[34] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.2 (t, 3H), 1.4-1.6 (m, 2H), 1.85-2.06 (m, 5H), 2.3 (s, 6H), 2.7 (q, 2H), 2.92 (d, 2H), 3.32 (s, 3H), 4.02 (d, 2H), 7.1-7.3 (m, 4H), 7.51(s, 1H), 8.65 (s, 1H), 9.77 (s, 1H), 11.97 (s, 1H); Mass Spectrum: $M+H^+$ 464.

[35] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.51 (m, 2H), 1.9–2.1 (m, 5H), 2.3 (s, 9H), 2.95 (d, 2H), 3.52 (s, 3H), 4.02 (d, 2H), 7.23 (s, 1H), 7.25 (s, 2H), 7.37 (s, 1H), 8.67 (s, 1H), 9.32 (s, 1H), 11.82 (s, 1H); Mass Spectrum: $M+H^+$ 528 and 530.

[36] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4–1.56 (m, 2H), 1.84–2.05 (m, 5H), 2.3 (s, 3H), 2.38 (s, 3H), 2.9 (d, 2H), 3.44 (s, 3H), 4.03 (d, 2H), 7.19 (d, 2H), 7.22 (s, 1H), 7.33 (t, 1H), 7.47 (s, 1H), 8.70 (s, 1H), 9.67 (s, 1H), 12.21 (s, 1H); Mass Spectrum: $M+H^+$ 470.

[37] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.81 (s, 4H), 2.17 (m, 2H), 2.57 (s, 4H), 2.7 (t, 2H), 3.77 (s, 3H), 4.26 (t, 2H), 7.23–7.45 (m, 2H), 7.38–7.45 (m, 2H), 8.7 (s, 1H), 8.96 (s, 1H), 12.23 (s, 1H); Mass Spectrum: $M+H^+$ 524 and 526.

The 4-amino-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 3-pyrrolidin-1-ylpropyl chloride (Chemical Abstracts, volume 128, no. 227441; PCT Patent Application WO 98/13354) using an analogous procedure to that described in the second last paragraph of Note [38] below to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline; NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H), 2.18 (m, 2H), 2.57 (s, 4H), 2.69 (t, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.16 (m, 1H), 7.28–7.36 (m, 2H), 7.44 (m, 1H), 7.57 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 476 & 478.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] below to give the required starting material; NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H), 2.14 (m, 2H), 2.54 (t, 4H), 2.67 (t, 2H), 3.96 (s, 3H), 4.23 (t, 2H), 5.54 (s, 2H), 6.91 (s, 1H), 7.23 (s, 1H), 8.52 (s, 1H); Mass Spectrum: $M+H^+$ 303.

[38] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.68 (s, 4H), 2.11 (m, 2H), 2.3 (s, 3H), 2.4–2.6 (m, 6H), 3.72 (s, 3H), 4.24 (t, 2H), 7.31 (s, 2H), 7.43 (s, 2H), 8.71 (s, 1H), 9.07 (s, 1H), 12.27 (s, 1H); Mass Spectrum: $M+H^+$ 553, 555 and 557.

The 4-amino-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline used as a starting material was prepared as follows :-

A mixture of 7-acetoxy-6-methoxyquinazolin-4-one (International Patent Application WO 96/15118, Example 17 thereof; 15 g), thionyl chloride (225 ml) and DMF (5 ml) was stirred and heated to 90°C for 4 hours. The mixture was cooled to ambient temperature and the thionyl chloride was evaporated. The material so obtained was dissolved in toluene and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic solution was dried over magnesium sulphate and evaporated. There was thus obtained 7-acetoxy-4-chloro-6-methoxyquinazoline (13.2 g) which was used without further purification.

A mixture of the material so obtained was reacted with 2-bromo-4-fluorophenol using an analogous procedure to that described in the second last paragraph of the portion of Example 1 above which is concerned with the preparation of starting materials. There was thus obtained 7-acetoxy-4-(2-bromo-4-fluorophenoxy)-6-methoxyquinazoline (14.7 g).

A mixture of a portion (3 g) of the material so obtained, concentrated ammonium hydroxide solution (0.88 g/ml, approximately 14M; 60 ml) and methanol (120 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was

triturated under diethyl ether. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (2.2 g); NMR Spectrum: ($DMSOd_6$) 3.99 (s, 3H), 7.25 (s, 1H), 7.39 (m, 1H), 7.54 (m, 2H), 7.78 (m, 1H), 8.47 (s, 1H), 10.82 (s, 1H);. Mass Spectrum: $M-H^-$ 363 & 365.

A mixture of 4-(2-bromo-4-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (0.94 g), 3-(4-methylpiperazin-1-yl)propyl chloride (0.5 g), potassium carbonate (1.42 g) and DMF (20 ml) was stirred and heated to 65°C for 16 hours. The mixture was filtered and evaporated. The resulting oil was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 2M methanolic ammonia solution as eluent. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (0.84 g); NMR Spectrum: ($CDCl_3$) 1.72 (s, 4H), 2.13 (m, 2H), 2.31 (s, 3H), 2.4–2.6 (m, 6H), 4.05 (s, 3H), 4.29 (t, 2H), 7.16 (m, 1H), 7.3 (s, 1H), 7.35 (s, 1H), 7.44 (m, 1H), 7.57 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 505 & 507.

A mixture of the material so obtained, liquid ammonia (1 ml) and a 2M solution of ammonia in isopropanol (15 ml) was sealed in a Carius tube and heated to 120°C for 16 hours. The mixture was cooled and evaporated. The residue was stirred under a 2N aqueous sodium hydroxide solution (200 ml) for 1 hour. The resultant solid was isolated and washed in turn with water (400 ml) and with methyl tert-butyl ether. There was thus obtained the required starting material (0.55 g); NMR Spectrum: ($CDCl_3$) 1.81 (s, 4H), 2.1 (m, 2H), 2.29 (s, 3H), 2.4–2.6 (m, 6H), 3.96 (s, 3H), 4.22 (t, 2H), 5.46 (s, 2H), 6.9 (s, 1H), 7.22 (s, 1H), 8.51 (s, 1H); Mass Spectrum: $M+H^+$ 332.

The 3-(4-methylpiperazin-1-yl)propyl chloride used as an intermediate was prepared by the reaction of 1-methylpiperazine with 1-bromo-3-chloropropane using an analogous procedure to that described in Note [42] hereinafter for the preparation of 3-morpholinopropyl chloride.

[39] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42 (q, 2H), 1.58 (m, 4H), 2.09 (m, 2H), 2.38 (s, 4H), 2.49 (t, 2H), 3.63 (s, 3H), 4.23 (t, 2H), 7.18–7.27 (m, 2H), 7.37 (m, 2H), 7.41 (s, 1H), 8.71 (s, 1H), 9.3 (s, 1H), 12.34 (s, 1H); Mass Spectrum: $M+H^+$ 504 and 506.

[40] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.84 (m, 4H), 2.17 (m, 2H), 2.56 (s, 4H), 2.68 (t, 2H), 3.69 (s, 3H), 4.28 (t, 2H), 6.99 (t, 2H), 7.2–7.3 (m, 2H), 7.38 (s, 1H), 8.71 (s, 1H), 9.3 (s, 1H), 12.04 (s, 1H); Mass Spectrum: $M+H^+$ 458.

[41] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.43 (m, 2H), 1.57–1.76 (m, 4H), 2.12 (m, 2H), 2.47 (s, 4H), 2.54 (t, 2H), 3.7 (s, 3H), 4.23 (t, 2H), 6.94–7.03 (m, 2H), 7.2–7.31 (m, 2H), 7.37 (s, 1H), 8.71 (s, 1H), 9.26 (s, 1H), 12.03 (s, 1H); Mass Spectrum: $M+H^+$ 472.

[42] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.11 (m, 2H), 2.49 (br s, 4H), 2.57 (t, 2H), 3.73 (m, 7H), 4.26 (t, 2H), 7.0 (t, 2H), 7.27 (m, 1H), 7.3 (s, 1H), 7.38 (s, 1H), 8.73 (s, 1H), 9.24 (s, 1H), 12.04 (s, 1H); Mass Spectrum: $M+H^+$ 474.

The 4-amino-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 3-morpholinopropyl chloride using an analogous procedure to that described in the second last paragraph of Note [38] above to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline; NMR Spectrum: ($CDCl_3$) 2.13 (m, 2H), 2.49 (t, 4H), 2.58 (t, 2H), 3.74 (t, 4H), 4.06 (s, 3H), 4.29 (t, 2H), 7.15 (m, 1H), 7.31 (m, 1H), 7.37 (s, 1H), 7.43 (m, 1H), 8.58 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 492 & 494.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] above to give the required starting material; NMR Spectrum: ($CDCl_3$) 2.09 (m, 2H), 2.48 (t, 4H), 2.55 (t, 2H), 3.61 (t, 4H), 3.96 (s, 3H), 4.24 (t, 2H), 5.44 (s, 2H), 6.9 (s, 1H), 7.24 (s, 1H), 8.52 (s, 1H).

The 3-morpholinopropyl chloride used as an intermediate was prepared as follows :-

Morpholine (52.2 ml) and 1-bromo-3-chloropropane (30 ml) were taken up in dry toluene (180 ml) and stirred and heated to 70°C for 3 hours. The resultant precipitate was filtered off and the filtrate was evaporated to give an orange oil which was purified by vacuum distillation collecting fractions at 62°C/5mmHg and 58°C/2mmHg. The required compound was obtained as an oil (37.9 g); NMR Spectrum: 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H); M/s: $M+H^+$ 164.

[43] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.71 (s, 4H), 2.12 (m, 2H), 2.31 (s, 3H), 2.42–2.62 (m, 6H), 3.7 (s, 3H), 4.27 (t, 2H), 7.0 (m, 2H), 7.21–7.32 (m, 2H), 7.38 (s, 1H), 8.73 (s, 1H), 9.62 (s, 1H), 12.08 (s, 1H); Mass Spectrum: $M+H^+$ 487.

[44] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.46 (m, 2H), 1.64 (m, 4H), 2.55 (t, 4H), 2.9 (t, 2H), 3.68 (s, 3H), 4.3 (t, 2H), 6.95–7.04 (m, 3H), 7.28 (m, 1H), 7.4 (s, 1H), 8.73 (s, 1H), 9.38 (s, 1H), 12.1 (s, 1H); Mass Spectrum: $M+H^+$ 458.

[45] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.49 (m, 2H), 1.63 (m, 4H), 2.56 (t, 4H), 2.8 (t, 2H), 3.7 (s, 3H), 4.32 (t, 2H), 7.3 (s, 1H), 7.34 (s, 1H), 7.43 (s, 2H), 8.72 (s, 1H), 9.22 (s, 1H), 12.32 (s, 1H); Mass Spectrum: $M+H^+$ 524 and 526.

[46] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H), 2.15 (m, 2H), 2.53 (s, 4H), 2.66 (t, 2H), 3.58 (s, 3H), 4.25 (t, 2H), 7.29 (s, 1H), 7.32–7.45 (m, 3H), 7.54 (d, 1H), 8.68 (s, 1H), 9.38 (s, 1H), 12.55 (s, 1H); Mass Spectrum: $M+H^+$ 507.

[47] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.38 (s, 6H), 2.88 (t, 2H), 3.57 (s, 3H), 4.27 (t, 2H), 6.98 (t, 3H), 7.27 (s, 1H), 7.51 (s, 1H), 8.71 (s, 1H), 9.81 (s, 1H), 12.25 (s, 1H); Mass Spectrum: $M+H^+$ 418.

The 4-amino-6-methoxy-7-(2-dimethylaminoethoxy)quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 2-dimethylaminoethyl chloride using an analogous procedure to that described in the second last paragraph of Note [38] above to give 4-(2-bromo-4-fluorophenoxy)-7-(2-dimethylaminoethoxy)-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$) 2.39 (s, 6H), 2.9 (t, 2H), 4.04 (s, 3H), 4.31 (t, 2H), 7.22 (t, 1H), 7.32 (s, 1H), 7.41 (m, 2H), 7.52 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 436 & 438.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] above to give the required starting material; NMR Spectrum: ($DMSOd_6$) 2.21 (s, 6H), 2.68 (t, 2H), 3.87 (s, 3H), 4.14 (t, 2H), 7.07 (s, 1H), 7.37 (s, 2H), 7.55 (s, 1H), 8.22 (s, 1H); Mass Spectrum: $M+H^+$ 263.

[48] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.38 (s, 6H), 2.87 (t, 2H), 3.49 (s, 3H), 4.26 (t, 2H), 7.24 (s, 2H), 7.4 (d, 2H), 7.53 (s, 1H), 8.72 (s, 1H), 9.8 (s, 1H), 12.47 (s, 1H); Mass Spectrum: $M+H^+$ 450 and 452.

[49] The product gave the following data: NMR Spectrum: ($CDCl_3$) 3.47 (t, 2H), 3.74 (m, 4H), 3.89 (s, 3H), 4.33 (t, 2H), 4.42 (s, 1H), 7.01 (t, 3H), 7.28 (m, 2H), 8.0 (s, 1H), 8.73 (s, 1H), 11.9 (s, 1H); Mass Spectrum: $M+H^+$ 459.

The 4-amino-6-methoxy-7-[2-(2-oxoimidazolidin-1-yl)ethoxy]quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 2-(2-oxoimidazolidin-1-yl)ethyl chloride (Indian J. Chem. Sect. B, 1982, 21B, 928-940) using an analogous procedure to that described in the second last paragraph of Note [38] above to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[2-(2-oxoimidazolidin-

1-yl)ethoxy]quinazoline; NMR Spectrum: ($CDCl_3$) 3.47 (t, 2H), 3.75 (m, 4H), 4.05 (s, 3H), 4.35 (t, 2H), 4.47 (s, 1H), 7.21 (t, 1H), 7.30 (s, 1H), 7.41 (t, 2H), 7.54 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 477 & 479.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] above to give the required starting material; NMR Spectrum: ($DMSOd_6$) 3.23 (t, 2H), 3.48 (m, 4H), 3.87 (s, 3H), 4.2 (t, 2H), 6.4 (s, 1H), 7.1 (s, 1H), 7.4 (s, 2H), 7.58 (s, 1H), 8.23 (s, 1H); Mass Spectrum: $M+H^+$ 304.

[50] The product gave the following data: NMR Spectrum: ($CDCl_3$) 3.48 (t, 2H), 3.73 (m, 7H), 4.32 (t, 2H), 4.48 (s, 1H), 7.13 (m, 2H), 7.44 (t, 3H), 8.74 (s, 1H), 9.1 (s, 1H), 12.27 (s, 1H); Mass Spectrum: $M+H^+$ 491 and 493.

[51] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.87 (m, 4H), 2.71 (s, 4H), 3.06 (t, 2H), 3.58 (s, 3H), 4.33 (t, 2H), 7.1–7.27 (m, 2H), 7.36–7.46 (m, 3H), 8.73 (s, 1H), 9.5 (s, 1H), 12.37 (s, 1H); Mass Spectrum: $M+H^+$ 476 and 478.

The 4-amino-6-methoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 2-pyrrolidin-1-ylethyl chloride using an analogous procedure to that described in the second last paragraph of Note [38] above to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline; NMR Spectrum: ($CDCl_3$) 1.83 (m, 4H), 2.69 (m, 4H), 3.06 (t, 2H), 4.04 (s, 3H), 4.34 (t, 2H), 7.21 (t, 1H), 7.31 (s, 1H), 7.4 (t, 2H), 7.53 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 462 & 464.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] above to give the required starting material; NMR Spectrum: ($CDCl_3$) 1.7 (s, 4H), 2.5 (m, 4H), 2.83 (t, 2H), 3.87 (s, 3H), 4.19 (t, 2H), 7.07 (s, 1H), 7.39 (s, 2H), 7.56 (s, 1H), 8.23 (s, 1H); Mass Spectrum: $M+H^+$ 289.

[52] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.87 (s, 4H), 2.73 (s, 4H), 3.07 (t, 2H), 3.65 (s, 3H), 4.34 (t, 2H), 6.99 (t, 3H), 7.28 (m, 1H), 7.43 (s, 1H), 8.75 (s, 1H), 9.47 (s, 1H), 12.11 (s, 1H); Mass Spectrum: $M+H^+$ 444.

[53] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.6 (t, 4H), 2.92 (t, 2H), 3.58 (s, 3H), 3.74 (t, 4H), 4.28 (t, 2H), 7.11–7.27 (m, 2H), 7.37–7.45 (m, 3H), 8.73 (s, 1H), 9.47 (s, 1H), 12.36 (s, 1H); Mass Spectrum: $M+H^+$ 492 and 494.

The 4-amino-6-methoxy-7-(2-morpholinoethoxy)quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 2-morpholinoethyl chloride using an analogous procedure to that described in the second last paragraph of Note [38] above to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(2-morpholinoethoxy)quinazoline; NMR Spectrum: ($CDCl_3$) 2.63 (t, 4H), 2.98 (t, 2H), 3.76 (t, 4H), 4.06 (s, 3H), 4.34 (t, 2H), 7.22 (t, 1H), 7.32 (s, 1H), 7.41 (t, 2H), 7.52 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 478 & 480.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] above to give the required starting material; NMR Spectrum: ($DMSOd_6$) 2.5 (m, 4H), 2.75 (t, 2H), 3.58 (t, 4H), 3.87 (s, 3H), 4.2 (t, 2H), 7.09 (s, 1H), 7.39 (s, 2H), 7.58 (s, 1H), 8.24 (s, 1H); Mass Spectrum: $M+H^+$ 305.

[54] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.63 (t, 4H), 3.04 (t, 2H), 3.61 (s, 3H), 3.76 (t, 4H), 4.33 (t, 2H), 6.99 (t, 2H), 7.27 (m, 2H), 7.45 (s, 1H), 8.74 (s, 1H), 9.57 (s, 1H), 12.15 (s, 1H); Mass Spectrum: $M+H^+$ 460.

[55] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H), 2.15 (m, 2H), 2.33 (s, 6H), 2.57 (br s, 4H), 2.69 (t, 2H), 3.41 (s, 3H), 4.26 (t, 2H), 7.14(m, 3H), 7.28 (s, 1H), 7.5 (s, 1H), 8.66 (s, 1H), 9.66 (s, 1H), 11.95 (s, 1H); Mass Spectrum: $M+H^+$ 450.

[56] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.09 (m, 2H), 2.32 (s, 6H), 2.46 (t, 4H), 2.55 (t, 2H), 3.4 (s, 3H), 3.71 (t, 2H), 4.25 (t, 2H), 7.11 (m, 3H), 7.28 (s, 1H), 7.49 (s, 1H), 8.66 (s, 1H), 9.61 (s, 1H), 11.91 (s, 1H); Mass Spectrum: $M+H^+$ 466.

[57] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.72 (s, 4H), 2.1 (m, 2H), 2.3 (s, 3H), 2.33 (s, 6H), 2.4–2.6 (m, 6H), 3.4 (s, 3H), 4.23 (t, 2H), 7.16 (m, 3H), 7.28 (s, 1H), 7.49 (s, 1H), 8.66 (s, 1H), 9.64 (s, 1H), 11.91 (s, 1H); Mass Spectrum: $M+H^+$ 479.

[58] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.85 (m, 4H), 2.34 (s, 6H), 2.68 (s, 4H), 3.05 (t, 2H), 3.31 (s, 3H), 4.3 (t, 2H), 7.14 (m, 3H), 7.26 (s, 1H), 7.56 (s, 1H), 8.65 (s, 1H), 9.87 (s, 1H), 11.98 (s, 1H); Mass Spectrum: $M+H^+$ 436.

[59] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.47 (s, 2H), 1.64 (m, 4H), 2.32 (s, 6H), 2.55 (s, 4H), 2.91 (t, 2H), 3.36 (s, 3H), 4.32 (t, 2H), 7.14 (m, 3H), 7.26 (s, 1H), 7.54 (s, 1H), 8.66 (s, 1H), 9.79 (s, 1H), 11.98 (s, 1H); Mass Spectrum: $M+H^+$ 450.

[60] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.31 (s, 6H), 2.61 (m, 4H), 2.94 (t, 2H), 3.27 (s, 3H), 3.76 (t, 4H), 4.31 (t, 2H), 7.15 (m, 3H), 7.26 (s, 1H), 7.59 (s, 1H), 8.67 (s, 1H), 9.97 (s, 1H), 12.01 (s, 1H); Mass Spectrum: $M+H^+$ 452.

[61] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.33 (s, 6H), 3.35 (s, 3H), 3.46 (t, 2H), 3.72 (m, 4H), 4.28 (t, 2H), 4.67 (s, 1H), 7.14 (m, 3H), 7.25 (s, 1H), 7.61 (s, 1H), 8.67 (s, 1H), 9.91 (s, 1H), 11.98 (s, 1H); Mass Spectrum: $M+H^+$ 451.

[62] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.33 (s, 6H), 2.39 (s, 6H), 2.87 (t, 2H), 3.28 (s, 3H), 4.26 (t, 2H), 7.12 (m, 3H), 7.26 (s, 1H), 7.58 (s, 1H), 8.66 (s, 1H), 9.97 (s, 1H), 12.02 (s, 1H); Mass Spectrum: $M+H^+$ 410.

[63] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.81 (m, 4H), 2.16 (m, 2H), 2.31 (s, 6H), 2.59 (s, 4H), 2.7 (t, 2H), 3.52 (s, 3H), 4.26 (t, 2H), 7.27 (m, 3H), 7.39 (s, 1H), 8.67 (s, 1H), 9.34 (s, 1H), 11.83 (s, 1H); Mass Spectrum: $M+H^+$ 528 and 530.

[64] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.45 (q, 2H), 1.6 (m, 4H), 2.13 (m, 2H), 2.3 (s, 6H), 2.44 (s, 4H), 2.54 (t, 2H), 3.53 (s, 3H), 4.25 (t, 2H), 7.29 (m, 3H), 7.37 (s, 1H), 8.68 (s, 1H), 9.27 (s, 1H), 11.81 (s, 1H); Mass Spectrum: $M+H^+$ 542 and 544.

[65] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.12 (m, 2H), 2.3 (s, 6H), 2.5 (t, 4H), 2.58 (t, 2H), 3.5 (s, 3H), 3.5 (t, 4H), 4.27 (t, 2H), 7.22–7.29 (m, 3H), 7.41 (s, 1H), 8.67 (s, 1H), 9.44 (s, 1H), 11.87 (s, 1H); Mass Spectrum: $M+H^+$ 544 and 546.

[66] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.66 (s, 10H), 2.11 (m, 2H), 2.3 (s, 3H), 2.4–2.6 (m, 6H), 3.58 (s, 3H), 4.24 (t, 2H), 7.25 (s, 3H), 7.34 (s, 1H), 8.67 (s, 1H), 9.2 (s, 1H), 11.79 (s, 1H); Mass Spectrum: $M+H^+$ 557 and 559.

[67] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.49 (m, 2H), 1.66 (m, 4H), 2.31 (s, 6H), 2.54 (t, 4H), 2.9 (t, 2H), 3.5 (s, 3H), 4.32 (t, 2H), 7.28 (m, 3H), 7.41 (s, 1H), 8.69 (s, 1H), 9.44 (s, 1H), 11.9 (s, 1H); Mass Spectrum: $M+H^+$ 528 and 530.

[68] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.3 (s, 6H), 2.64 (t, 4H), 2.95 (t, 2H), 3.41 (s, 3H), 3.77 (t, 4H), 4.33 (t, 2H), 7.27 (s, 3H), 7.48 (s, 1H), 8.69 (s, 1H), 9.71 (s, 1H), 11.97 (s, 1H); Mass Spectrum: $M+H^+$ 530 and 532.

[69] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.29 (s, 6H), 3.47 (t, 2H), 3.62 (s, 3H), 3.75 (m, 4H), 4.33 (t, 2H), 4.44 (s, 1H), 7.28 (m, 3H), 7.39 (s, 1H), 8.68 (s, 1H), 9.18 (s, 1H), 11.77 (s, 1H); Mass Spectrum: $M+H^+$ 529 and 531.

[70] The product gave the following data: NMR Spectrum: ($CDCl_3$) 3.39 (s, 3H), 3.54 (s, 3H), 3.6 (m, 2H), 3.75 (m, 2H), 3.98 (t, 2H), 4.33 (t, 2H), 7.24 (m, 2H), 7.41 (m, 2H), 7.48 (s, 1H), 8.73 (s, 1H), 9.68 (s, 1H), 12.46 (s, 1H); Mass Spectrum: $M+H^+$ 481 and 483.

The 4-amino-6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]quinazoline used as a starting material was prepared as follows :-

4-(4-Bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was reacted with 2-(2-methoxyethoxy)ethyl tosylate (prepared from 2-(2-methoxyethoxy)ethanol and tosyl chloride) using an analogous procedure to that described in the second last paragraph of Note [38] above to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]quinazoline; NMR Spectrum: ($CDCl_3$) 3.4 (s, 3H), 3.6 (m, 2H), 3.76 (m, 2H), 4.03 (m, 5H), 4.39 (t, 2H), 7.21 (m, 1H), 7.34 (s, 1H), 7.41 (t, 2H), 7.51 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 467 & 469.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [38] above to give the required starting material; NMR Spectrum: ($DMSOd_6$) 3.23 (s, 3H), 3.46 (m, 2H), 3.6 (m, 2H), 3.79 (t, 2H), 3.88 (s, 3H), 4.2 (t, 2H), 7.08 (s, 1H), 7.39 (s, 2H), 7.57 (s, 1H), 8.23 (s, 1H); Mass Spectrum: $M+H^+$ 294.

[71] The product gave the following data: NMR Spectrum: ($CDCl_3$) 3.39 (s, 3H), 3.6 (m, 5H), 3.77 (m, 2H), 4.01 (t, 2H), 4.36 (s, 1H), 7.01 (t, 3H), 7.26 (m, 2H), 7.46 (s, 1H), 8.72 (s, 1H), 9.58 (s, 1H), 12.16 (s, 1H); Mass Spectrum: $M+H^+$ 449.

[72] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.31 (s, 6H), 3.27 (s, 3H), 3.4 (s, 3H), 3.6 (m, 2H), 3.75 (m, 2H), 3.97 (t, 2H), 4.34 (t, 2H), 7.14 (m, 3H), 7.26 (s, 1H), 7.57 (s, 1H), 8.66 (s, 1H), 9.95 (s, 1H), 12.03 (s, 1H); Mass Spectrum: $M+H^+$ 441.

[73] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4–1.54 (m, 2H), 1.82–2.03 (m, 5H), 2.3 (s, 3H), 2.91 (d, 2H), 3.53 (s, 3H), 4.02 (d, 2H), 7.26 (m, 1H), 7.31–7.47 (m, 3H), 7.55 (d, 1H), 8.68 (s, 1H), 9.49 (s, 1H), 12.6 (s, 1H); Mass Spectrum: $M+H^+$ 508.

[74] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.82 (m, 4H), 2.66 (m, 4H), 3.0 (t, 2H), 4.27 (t, 2H), 7.2-7.4 (m, 3H), 7.5 (d, 2H), 8.05 (d, 1H), 8.78 (s, 1H), 9.1 (br s, 1H), 12.07 (br s, 1H); Mass Spectrum: $M+H^+$ 446 and 448.

The 4-amino-7-(2-pyrrolidin-1-ylethoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 7-hydroxy-4-methylthioquinazoline (6 g) and a saturated solution of ammonia gas in methanol (225 ml) was sealed in a pressure vessel and heated at 120°C for 40 hours. The mixture was cooled to ambient temperature and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-amino-7-hydroxyquinazoline (4.9 g); NMR Spectrum: ($DMSOd_6$) 6.9 (s, 1H), 6.9 (d, 1H), 9.5 (br s, 2H), 8.04 (d, 1H), 8.24 (s, 1H).

Diethyl azodicarboxylate (3.3 ml) was added dropwise to a stirred mixture of 4-amino-7-hydroxyquinazoline (5.16 g), triphenylphosphine (16.8 g) and methylene chloride (260 ml) which had been cooled to 0°C. The mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 50:45:5 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide (9.7 g); NMR Spectrum: ($DMSOd_6$) 6.85 (s, 1H), 7.05 (m, 1H), 7.5-7.95 (m, 15H), 8.12 (s, 1H), 8.5 (d, 1H), 10.3 (br s, 1H).

3,3-Dimethyl-1,2,5-thiadiazolidine-1,1-dioxide (J. Med. Chem. 1994, 37, 3023; 0.39 g) was added portionwise to a stirred mixture of triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide (0.2 g), N-(2-hydroxyethyl)pyrrolidine (0.081 g) and methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 1 hour. Diethyl ether (10 ml) was added and the mixture was filtered through diatomaceous earth. The filtrate was evaporated and the residue was purified by column chromatography on silica using as eluent a 48:50:2 mixture of methylene chloride, ethyl acetate and a saturated ammonia solution in methanol. There was thus obtained triphenylphosphine N-[7-(2-pyrrolidin-1-ylethoxy)quinazolin-4-yl]imide (0.084 g); NMR Spectrum: ($DMSOd_6$ + CF_3CO_2D) 1.93 (m, 2H), 2.08 (m, 2H), 3.2 (m, 2H), 3.66 (m, 2H), 3.73 (m, 2H), 4.5 (m, 2H), 7.16 (s, 1H), 7.42 (m, 1H), 7.6-8.0 (m, 15H), 8.62 (s, 1H), 8.71 (d, 1H); Mass Spectrum: $M+H^+$ 519.

A mixture of a portion (0.42 g) of the material so obtained, a 1N aqueous acetic acid solution (2 ml) and ethanol (2 ml) was stirred and heated to 100°C for 15 hours. The mixture was evaporated and the residue was dried under vacuum. There was thus obtained 4-amino-7-(2-pyrrolidin-1-ylethoxy)quinazoline in quantitative yield and this was used directly without future purification.

[75] The product gave the following data: Mass Spectrum: $M+H^+$ 426 and 428.

[76] The product gave the following data: Mass Spectrum: $M+H^+$ 412 and 414.

[77] The product gave the following data: Mass Spectrum: $M+H^+$ 480 and 482.

[78] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4-1.7 (m, 6H), 2.55 (br s, 4H), 2.85 (t, 2H), 4.25 (t, 2H), 7.1-7.38 (m, 4H), 7.48 (d, 2H), 8.05 (d, 2H), 8.8 (s, 1H), 9.02 (br s, 1H); Mass Spectrum: $M+H^+$ 460 and 462.

The 4-amino-7-(2-piperidinoethoxy)quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with N-(2-hydroxyethyl)piperidine using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-[7-(2-piperidinoethoxy)quinazolin-4-yl]imide in 21% yield; Mass Spectrum: $M+H^+$ 533. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: $M+H^+$ 273.

[79] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.45 (br m, 2H), 1.55-1.75 (m, 4H), 2.55 (br s, 4H), 2.85 (t, 2H), 4.28 (t, 2H), 7.05 (m, 2H), 7.12-7.4 (m, 4H), 8.15 (d, 1H), 8.8 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 428.

[80] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4-1.72 (m, 6H), 2.42 (s, 3H), 2.55 (br s, 4H), 2.85 (t, 2H), 4.3 (t, 2H), 7.12-7.32 (m, 5H), 8.35 (d, 1H), 7.95 (d, 1H), 8.6 (s, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 440 and 442.

[81] The product gave the following data: Mass Spectrum: $M+H^+$ 426 and 428.

[82] The product gave the following data: Mass Spectrum: $M+H^+$ 494 and 496.

[83] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.32 (s, 3H), 2.5 (br s, 4H), 2.7 (br s, 4H), 2.9 (t, 2H), 4.3 (t, 2H), 7.2 (d, 1H), 7.25-7.4 (m, 3H), 7.47 (d, 2H), 8.05 (d, 1H), 8.8 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 475 and 477.

The 4-amino-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with 1-(2-hydroxyethyl)-4-methylpiperazine using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-{7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazolin-4-yl}imide in 30% yield; Mass Spectrum: $M+H^+$ 548. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: $M+H^+$ 288.

The 1-(2-hydroxyethyl)-4-methylpiperazine used as a starting material was prepared as follows :-

A mixture of 2-bromoethanol (2.36 g), N-methylpiperazine (1.26 g), potassium carbonate (5.0 g) and ethanol (150 ml) was stirred and heated to reflux for 18 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under a mixture of methylene chloride and acetone. The resultant

mixture was filtered and the filtrate was evaporated to give the required starting material as an oil (0.87 g); NMR Spectrum: ($CDCl_3$) 2.18 (s, 3H), 2.3-2.7 (br m, 8H), 2.56 (t, 2H), 3.61 (t, 2H).

[84] The product gave the following data: Mass Spectrum: $M+H^+$ 455 and 457.

[85] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.3 (s, 3H), 2.48 (br s, 4H), 2.65 (br s, 4H), 2.9 (t, 2H), 4.3 (t, 2H), 7.1 (m, 1H), 7.2-7.4 (m, 4H), 7.45 (d, 1H), 7.97 (d, 1H), 8.35 (br s, 1H), 8.45 (d, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 441 and 443.

[86] The product gave the following data: Mass Spectrum: $M+H^+$ 509 and 511.

[87] The product gave the following data: Mass Spectrum: $M+H^+$ 460 and 462.

The 4-amino-7-(N-methylpiperidin-3-ylmethoxy)quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with 3-hydroxymethyl-N-methylpiperidine using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-[7-(N-methylpiperidin-3-ylmethoxy)quinazolin-4-yl]imide in 49% yield; Mass Spectrum: $M+H^+$ 533. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: $M+H^+$ 273.

[88] The product gave the following data: Mass Spectrum: $M+H^+$ 428.

[89] The product gave the following data: Mass Spectrum: $M+H^+$ 440 and 442.

[90] The product gave the following data: Mass Spectrum: $M+H^+$ 426 and 428.

[91] The product gave the following data: Mass Spectrum: $M+H^+$ 494 and 496.

[92] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.85 (br s, 4H), 2.1 (m, 2H), 2.6 (br s, 4H), 2.7 (t, 2H), 4.2 (t, 2H), 7.15 (d, 1H), 7.2-7.4 (m, 3H), 7.5 (d, 2H), 8.1 (d, 1H), 8.8 (s, 1H), 9.2 (br s, 1H); Mass Spectrum: $M+H^+$ 460 and 462.

The 4-amino-7-(3-pyrrolidin-1-ylpropoxy)quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with N-(3-hydroxypropyl)pyrrolidine using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-[7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]imide in 42% yield; Mass Spectrum: $M+H^+$ 533. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described

in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: $M+H^+$ 273.

The N-(3-hydroxypropyl)pyrrolidine used as a starting material was prepared as follows :-

A mixture of 3-chloropropanol (66 g), pyrrolidine (50 g), potassium carbonate (145 g) and acetonitrile (1 L) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by distillation to give the required starting material as an oil (62 g); NMR Spectrum: ($CDCl_3$) 1.6-1.8 (m, 6H), 2.55 (br s, 4H), 2.75 (t, 2H), 3.85 (t, 2H), 5.5 (br s, 1H).

[93] The product gave the following data: Mass Spectrum: $M+H^+$ 428.

[94] The product gave the following data: Mass Spectrum: $M+H^+$ 440 and 442.

[95] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.82 (br s, 4H), 2.1 (m, 2H), 2.55 (br s, 4H), 2.65 (t, 4H), 4.25 (t, 2H), 7.1 (m, 1H), 7.2-7.45 (m, 4H), 7.5 (d, 1H), 7.95 (d, 1H), 8.15 (s, 1H), 8.45 (d, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 426 and 428.

[96] The product gave the following data: NMR Spectrum: ($CDCl_3$) 7.2 (m, 1H), 7.25-7.4 (m, 3H), 7.5 (s, 1H), 8.0 (d, 1H), 8.8 (s, 1H), 8.95 (br s, 1H); Mass Spectrum: $M+H^+$ 494 and 496.

[97] The product gave the following data: Mass Spectrum: $M+H^+$ 444.

The 4-amino-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with N-(3-hydroxypropyl)morpholine using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-[7-(3-morpholinopropoxy)quinazolin-4-yl]imide and the material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: $M+H^+$ 289.

[98] The product gave the following data: Mass Spectrum: $M+H^+$ 456 and 458.

[99] The product gave the following data: Mass Spectrum: $M+H^+$ 510 and 512.

[100] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.35 (s, 3H), 2.35-2.75 (m, 8H), 2.6 (t, 2H), 4.22 (t, 2H), 7.12 (m, 1H), 7.2-7.38 (m, 3H), 7.5 (d, 2H), 8.15 (d, 1H), 8.8 (s, 1H), 9.5 (br s, 1H); Mass Spectrum: $M+H^+$ 489 and 491.

The 4-amino-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-{7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}imide in 44% yield; Mass Spectrum: $M+H^+$ 562. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: $M+H^+$ 302.

The 1-(3-hydroxypropyl)-4-methylpiperazine used as a starting material was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation to give the required starting material as an oil; NMR Spectrum: ($CDCl_3$) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

[101] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.07 (t, 2H), 2.32 (s, 3H), 2.3-2.75 (m, 8H), 2.6 (t, 2H), 4.22 (t, 2H), 7.1 (m, 1H), 7.2-7.45 (m, 4H), 7.5 (d, 1H), 8.05 (d, 1H), 8.45 (d, 1H), 8.55 (s, 1H), 8.85 (s, 1H); Mass Spectrum: $M+H^+$ 455 and 457.

[102] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.3 (s, 3H), 2.35-2.7 (m, 8H), 2.6 (t, 2H), 4.2 (t, 2H), 7.15 (m, 1H), 7.2-7.4 (m, 3H), 7.5 (s, 1H), 8.05 (d, 1H), 8.8 (s, 1H), 9.02 (br s, 1H); Mass Spectrum: $M+H^+$ 523 and 525.

[103] The product gave the following data: Mass Spectrum: $M+H^+$ 492.

[104] The product gave the following data: Mass Spectrum: $M+H^+$ 504 and 506.

[105] The product gave the following data: Mass Spectrum: $M+H^+$ 558 and 560.

[106] The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.55 (m, 2H), 4.15 (t, 2H), 4.7 (t, 2H), 7.2-7.4 (m, 4H), 7.5 (s, 1H), 7.58 (s, 1H), 7.65 (s, 1H), 7.95 (d, 1H), 8.55 (d, 1H), 8.8 (s, 1H); Mass Spectrum: $M+H^+$ 492 and 494.

The 4-amino-7-[3-(1,2,3-triazol-1-yl)propoxy]quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with N^1-(3-hydroxypropyl)-1,2,3-triazole using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-{7-[3-(1,2,3-triazol-

1-yl)propoxy]quinazolin-4-yl}imide in 18% yield; Mass Spectrum: M+H$^+$ 531. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: M+H$^+$ 271.

The N^1-(3-hydroxypropyl)-1,2,3-triazole used as a starting material was prepared as follows :-

A mixture of 1,2,3-triazole (5 g), ethyl acrylate (7.8 ml) and pyridine (50 drops) was stirred and heated to 90°C for 4 hours. The mixture was cooled to ambient temperature and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and diethyl ether as eluent. There was thus obtained ethyl 1,2,3-triazol-1-ylpropanoate (8.96 g); NMR Spectrum: ($CDCl_3$) 1.25 (t, 3H), 2.95 (t, 2H), 4.15 (q, 2H), 4.7 (t, 2H), 7.65 (s, 1H), 7.7 (s, 1H).

A solution of the material so obtained in THF (50 ml) was added dropwise to a suspension of lithium aluminium hydride (3 g) in THF (250 ml) which had been cooled to 0°C. The mixture was stirred at 5°C for 1 hour and at ambient temperature for a further hour. The mixture was cooled to 0°C and 4N aqueous sodium hydroxide solution (30 ml) was added dropwise. The mixture was filtered and the filtrate was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 47:3 mixture of methylene chloride and methanol as eluent. There was thus obtained N^1-(3-hydroxypropyl)-1,2,3-triazole (6.2 g); NMR Spectrum: ($CDCl_3$) 2.1-2.2 (m, 3H), 3.65 (m, 2H), 4.6 (t, 2H), 7.6 (s, 1H), 7.72 (s, 1H).

[107] The product gave the following data: Mass Spectrum: M+H$^+$ 440.

The 4-amino-7-[(*E*)-4-pyrrolidin-1-ylbut-2-en-1-yloxy]quinazoline used as a starting material was prepared as follows :-

Triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide was reacted with (*E*)-4-pyrrolidin-1-ylbut-2-en-1-ol using an analogous procedure to that described in the second last paragraph of Note [74] above to give triphenylphosphine N-{7-[(*E*)-4-pyrrolidin-1-ylbut-2-en-1-yloxy]quinazolin-4-yl}imide in 38% yield; Mass Spectrum: M+H$^+$ 545. The material so obtained was reacted with aqueous acetic acid using an analogous procedure to that described in the last paragraph of Note [74] above to give the required starting material; Mass Spectrum: M+H$^+$ 285.

The (*E*)-4-pyrrolidin-1-ylbut-2-en-1-ol used as a starting material was prepared as follows :-

Thionyl chloride (9.3 ml) was added portionwise to a stirred mixture of 2-butyne-1,4-diol (10 g), pyridine (10.3 ml) and toluene (15 ml) which had been cooled to 0°C. The mixture was stirred at ambient temperature for 3.5 hours and then poured onto a mixture of ice and water. The mixture was extracted with diethyl ether. The organic extract was washed with a saturated aqueous sodium bicarbonate solution and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 7:3 mixture of petroleum ether (b.p. 40-60°C) and diethyl ether as eluent. There was thus obtained 4-chlorobut-2-yn-1-ol (4.74 g); NMR Spectrum: ($CDCl_3$) 1.68 (t, 1H), 4.18 (d, 2H), 4.33 (d, 2H).

Pyrrolidine (7.8 ml) was added dropwise to a solution of 4-chlorobut-2-yn-1-ol (4.74 g) in toluene (40 ml) and the resultant mixture was stirred and heated to 60°C for 1 hour. The mixture was evaporated and the residue was purified by column chromatography on silica using a 24:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-pyrrolidin-1-ylbut-2-yn-1-ol (4.3 g); NMR Spectrum: ($CDCl_3$) 1.82 (t, 4H), 2.63 (t, 4H), 3.44 (t, 2H), 4.29 (t, 2H).

A solution of the material so obtained in THF (20ml) was added dropwise to a suspension of lithium aluminium hydride (2.35 g) in THF (8 ml) and the mixture was stirred and heated to 60°C for 2 hours. The mixture was cooled to 5°C and 2N aqueous sodium hydroxide solution (28 ml) was slowly added. The resulting suspension was filtered and the filtrate was evaporated. The residue was dissolved in a mixture of methylene chloride and ethyl acetate, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on aluminium oxide using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained (*E*)-4-pyrrolidin-1-ylbut-2-en-1-ol (3.09 g); NMR Spectrum: ($CDCl_3$) 1.82 (m, 4H), 2.61 (m, 4H), 3.17 (m, 2H), 4.13 (s, 2H), 5.84 (m, 2H).

[108] The product gave the following data: Mass Spectrum: $M+H^+$ 452 and 454.

[109] The product gave the following data: Mass Spectrum: $M+H^+$ 438 and 440.

[110] DMF was used as the reaction solvent. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.5-1.65 (m, 2H), 1.68-1.74 (m, 2H), 1.92 (t, 2H), 1.97 (t, 2H), 2.05 (m, 1H), 2.45 (t, 2H), 2.88 (d, 2H), 3.98 (s, 3H), 4.22 (t, 2H), 6.68 (s, 1H), 7.18 (s, 1H), 7.3 (s, 1H), 7.4 (t, 1H), 7.61 (d, 2H), 8.07 (s, 1H), 8.7 (s, 1H), 10.62 (s, 1H), 12.08 (s, 1H); Mass Spectrum: $M+H^+$ 547 and 549.

The 4-amino-7-[3-(4-carbamoylpiperidin-1-yl)propoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g) and Gold's reagent (7.4 g) in dioxane (100 ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added to the reaction mixture and it was heated for a further 3 hours. The mixture was evaporated to dryness, water was added to the residue and the solid was filtered off, washed with water and dried. Recrystallisation of the solid from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g, 84%).

7-Benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3 g) was taken up in thionyl chloride (440 ml) and DMF (1.75ml) and heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. There was thus obtained 7-benzyloxy-4-chloro-6-methoxyquinazoline which was used without further purification; NMR Spectrum: 4.88 (s, 3H), 5.25 (s, 2H), 7.44 (s, 1H), 7.49 (s, 1H), 7.32-7.52 (m, 5H), 8.83 (s, 1H).

A mixture of the crude 7-benzyloxy-4-chloro-6-methoxyquinazoline, potassium carbonate (50 g) and 4-bromo-2-fluorophenol (10 ml) in DMF (500 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature and was poured into water (2L). The resultant solid was isolated and washed with water. The solid was dissolved in methylene chloride and filtered. The filtrate was treated with decolourising charcoal, boiled for a few minutes then filtered. The filtrate was evaporated to give a solid residue which was triturated under diethyl ether. There was thus obtained 7-benzyloxy-4-(4-bromo-2-fluorophenoxy)-6-methoxyquinazoline.

A mixture of the material so obtained and trifluoroacetic acid (15 ml) was stirred and heated to reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the mixture was evaporated. The residue was triturated under diethyl ether. The precipitate was collected by filtration and dried to give 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (20.3 g) which was used without further purification.

A mixture of 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (18.2 g), 1,3-dibromopropane (80 ml), potassium carbonate (42 g) and DMF (1.2 L) was stirred and heated to 45°C for 16 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The product

so obtained was stirred under diethyl ether (150 ml) and the resultant solid was isolated. There was thus obtained 4-(4-bromo-2-fluorophenoxy)-7-(3-bromopropoxy)-6-methoxyquinazoline (14.4 g); NMR Spectrum: ($DMSOd_6$) 2.35 (m, 2H), 3.69 (t, 2H), 3.98 (s, 3H), 4.31 (t, 2H), 7.4-7.6 (m, 4H), 7.78 (d, 1H), 8.78 (s, 1H); Mass Spectrum: $M+H^+$ 485, 487 and 489.

A mixture of a portion (2.4 g) of the material so obtained, piperidine-4-carboxamide (0.82 g), potassium carbonate (3.46 g) and DMF (40 ml) was stirred and heated to 45°C for 20 hours. The resultant solid was isolated, washed in turn with DMF and with water and dried. There was thus obtained 4-(4-bromo-2-fluorophenoxy)-7-[3-(4-carbamoylpiperidin-1-yl)propoxy]-6-methoxyquinazoline (2.5 g); NMR Spectrum: ($DMSOd_6$) 1.45-1.7 (m, 4H), 1.82-2.1 (m, 5H), 2.22 (t, 2H), 2.86 (m, 2H), 3.96 (s, 3H), 4.03 (t, 2H), 6.65 (s, 1H), 7.14 (s, 1H), 7.38 (s, 1H), 7.42-7.55 (m, 3H), 7.78 (d, 1H), 8.53 (s, 1H); Mass Spectrum: $M+H^+$ 533 and 535.

A mixture of the material so obtained and a saturated solution of ammonia in isopropanol (100 ml) was sealed in a Carius tube and heated at 130°C for 20 hours. The mixture was cooled and the solvent was evaporated. The residue was stirred with 2N aqueous sodium hydroxide solution (20 ml) for 1 hour. The solid was isolated and washed in turn with water and with methanol. There was thus obtained 4-amino-7-[3-(4-carbamoylpiperidin-1-yl)propoxy]-6-methoxyquinazoline (0.85 g); NMR Spectrum: ($DMSOd_6$) 1.4-1.7 (m, 4H), 1.8-2.1 (m, 5H), 2.4 (t, 2H), 2.68 (d, 2H), 3.86 (s, 3H), 4.1 (t, 2H), 6.66 (s, 1H), 7.03 (s, 1H), 7.15 (s, 1H), 7.33 (s, 2H), 7.53 (s, 1H), 8.23 (s, 1H); Mass Spectrum: $M+H^+$ 360.

[111] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.5-1.7 (m, 4H), 1.8-2.1 (m, 5H), 2.4 (t, 2H), 2.88 (d, 2H), 2.94 (s, 3H), 4.0 (t, 2H), 6.65 (s, 1H), 7.1-7.5 (m, 5H), 8.05 (s, 1H), 8.66 (s, 1H), 10.6 (s, 1H), 11.8 (s, 1H); Mass Spectrum: $M+H^+$ 515.

[112] THF was added as a co-solvent. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.6-2.3 (m, 9H), 2.35 (s, 6H), 2.53 (t, 2H), 2.99 (d, 2H), 3.42 (s, 3H), 4.25 (t, 2H), 5.55 (s, 2H), 7.11 (s, 3H), 7.29 (s, 1H), 7.55 (s, 1H), 8.64 (s, 1H), 9.7 (s, 1H), 11.9 (s, 1H); Mass Spectrum: $M+H^+$ 507.

[113] DMF was used as the reaction solvent. The product was precipitated from the reaction mixture as a 1:1 adduct with DMF. This gave the following data: NMR Spectrum: ($CDCl_3$) 1.7-2.3 (m, 9H), 2.37 (s, 3H), 2.54 (t, 2H), 2.88 (s, 3H), 2.95 (s, 3H), 3.0 (m, partially obscured by DMF), 3.5 (s, 3H), 4.25 (t, 2H), 5.61 (broad d, 2H), 7.16-7.32 (m, 4H), 7.55 (s, 1H), 8.02 (s, 1H), 8.67 (s, 1H), 9.8 (s, 1H), 12.4 (s, 1H); Mass Spectrum: $M+H^+$ 527 and 529.

[114] Acetonitrile plus a few drops of DMF was used as the reaction solvent and the reaction mixture was heated to 45°C for 3 hours. The product which was precipitated from the reaction mixture was isolated, washed with acetonitrile and diethyl ether and dried under vacuum. The product gave the following data: Mass Spectrum: $M+H^+$ 440 and 442.

The 4-amino-7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazoline used as a starting material was prepared as follows :-

Trifluoromethanesulphonic anhydride (0.05 ml) was added dropwise to a stirred mixture of triphenylphosphine N-(7-hydroxyquinazolin-4-yl)imide (0.1 g), pyridine (0.5 ml) and methylene chloride (1 ml) which had been cooled to 0°C. The reaction mixture was stirred at 0°C for 2 hours. A second portion (0.012 ml) of trifluoromethanesulphonic anhydride was added and the mixture was stirred at ambient temperature for 1.5 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic solution was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained triphenylphosphine N-(7-trifluoromethanesulphonyloxyquinazolin-4-yl)imide (0.078 g).

A solution of 3-(pyrrolidin-1-yl)-1-propyne (J. Amer. Chem. Soc., 1958, 80, 4609; 0.08 g) in DMF (0.2 ml) was added to a mixture of triphenylphosphine N-(7-trifluoromethanesulphonyloxyquinazolin-4-yl)imide (0.2 g), cuprous iodide (0.004 g), tetrakis(triphenylphosphine)palladium(0) (0.02 g), triethylamine (0.201 ml) and DMF (8 ml). The mixture was degassed carefully and placed under an atomsphere of argon. The reaction mixture was stirred and heated to 60°C for 2.5 hours. The mixture was cooled to ambient temperature and evaporated. The residue was partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained triphenylphosphine N-{7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazolin-4-yl}imide (0.18 g).

A mixture of the material so obtained, acetic acid (4 ml) and water (4 ml) was stirred and heated at 100°C for 15 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic solution was washed with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using initially a 9:1 mixture of methylene chloride and methanol and then a 19:1 mixture of methylene chloride and a

saturated solution of ammonia in methanol as eluent. There was thus obtained 4-amino-7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazoline (0.038 g); NMR Spectrum: ($DMSOd_6$) 1.75 (m, 4H), 2.6 (m, 4H), 3.65 (s, 2H), 7.45 (m, 1H), 7.25 (d, 1H), 7.85 (br s, 2H), 8.2 (d, 1H), 8.4 (s, 1H); Mass Spectrum: $M+H^+$ 253.

[115] DMF was used as the reaction solvent and 4-dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. The product was precipitated from the reaction mixture by the addition of a mixture of diethyl ether and water. The product was isolated and dried under vaccuum and gave the following data: NMR Spectrum: ($DMSOd_6$) 1.72 (m, 4H), 2.6 (m, 4H), 3.69 (s, 2H), 3.97 (s, 3H), 7.4 (m, 1H), 7.58 (m, 2H), 7.9 (s, 1H), 8.15 (s, 1H), 8.75 (s, 1H), 10.8 (s, 1H), 11.95 (s, 1H); Mass Spectrum: $M+H^+$ 470 and 472.

The 4-amino-6-methoxy-7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazoline used as a starting material was prepared as follows :-

Pyridine (1.13 ml) and a solution of trifluoromethanesulphonic anhydride (2.36 ml) in methylene chloride (10 ml) were added in turn to a stirred mixture of 4-(2-bromo-4-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (2.6 g) and methylene chloride (40 ml) which had been cooled in an ice bath to 0-5°C. The resultant mixture was stirred at ambient temperature for 4 hours. The mixture was washed in turn with dilute aqueous citric acid, water and a saturated aqueous sodium bicarbonate solution. The organic solution was dried over magnesium sulphate and evaporated. The residue was triturated under a 1:1 mixture of isohexane and diethyl ether. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline (2.58 g); NMR Spectrum: ($CDCl_3$) 4.13 (s, 3H), 7.14-7.5 (m, 3H), 7.81 (s, 1H), 7.91 (s, 1H), 8.7 (s, 1H); Mass Spectrum: $M+H^+$ 497 and 499.

A mixture of a portion (0.8 g) of the material so obtained, 3-(pyrrolidin-1-yl)-1-propyne (0.57 g), triethylamine (0.8 ml), triphenylphosphine (0.03 g), bis(triphenylphosphine)palladium(II) chloride (0.06 g), cuprous iodide (0.06 g) and THF (5 ml) was stirred and heated to reflux for 3 hours. Dilute aqueous potassium carbonate solution was added and the mixture was extracted with ethyl acetate. The organic solution was dried over sodium sulphate and evaporated. The residue was purified by column chromatography on silica using a 10:1 mixture of methylene chloride and ethanol as eluent. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazoline (0.55 g); NMR Spectrum: ($DMSOd_6$) 1.75 (m, 4H), 2.64 (m, 4H),

3.71 (s, 2H), 4.01 (s, 3H), 7.38-7.81 (m, 3H), 7.66 (s, 1H), 8.0 (s, 1H), 8.62 (s, 1H); Mass Spectrum: $M+H^+$ 456 & 458.

A mixture of the material so obtained and a 2M solution of ammonia in isopropanol (10 ml) was sealed in a Carius tube and heated to 130°C for 18 hours. The reaction mixture was evaporated. The residue was partitioned between ethyl acetate and a 1N aqueous potassium carbonate solution. The organic solution was washed with brine, dried over anhydrous sodium sulphate and evaporated. The residue was triturated under a 1:1 mixture of isohexane and diethyl ether. The resultant solid was isolated and dried. There was thus obtained 4-amino-6-methoxy-7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazoline (0.24 g); Mass Spectrum: $M+H^+$ 283.

[116] DMF was used as the reaction solvent and 4-dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.6 (m, 4H), 2.35 (m, 6H), 2.55 (m, 2H), 3.6 (m, 4H), 3.97 (s, 3H), 7.3-7.6 (m, 3H), 7.83 (s, 1H), 8.11 (s, 1H), 8.72 (s, 1H), 10.78 (s, 1H), 11.95 (s, 1H); Mass Spectrum: $M+H^+$ 528 and 530.

The 4-amino-6-methoxy-7-(6-morpholino-1-hexynyl)quinazoline used as a starting material was prepared as follows:

Using an analogous procedure to that described in the second last paragraph of Note [115] above, 6-morpholino-1-hexyne was reacted with 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(6-morpholino-1-hexynyl)quinazoline; NMR Spectrum: ($DMSOd_6$) 1.63 (m, 4H), 2.33 (m, 6H), 2.55(m, 2H), 3.56 (m, 4H), 4.0 (s, 3H), 7.35-7.8 (m, 3H), 7.65 (s, 1H), 7.96 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 514 and 516.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

6-Morpholino-1-hexyne was obtained by the reaction of 6-mesyloxy-1-hexyne with morpholine using an analogous procedure to that described in J. Heterocyclic Chemistry, 1994, 31, 1421.

[117] DMF was used as the reaction solvent and 4-dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.6 (m, 4H), 2.32 (m, 6H), 2.55 (m, 2H), 3.55 (m, 4H), 3.98 (s, 3H), 7.1-7.4 (m, 3H), 7.82 (s, 1H), 8.11 (s, 1H), 8.7 (s, 1H), 10.78 (s, 1H), 11.68 (s, 1H); Mass Spectrum: $M+H^+$ 496.

[118] DMF was used as the reaction solvent and 4-dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.55 (m, 2H), 1.85 (m, 2H), 2.28 (s, 3H), 2.56 (m, 2H), 3.9 (m, 2H), 3.96 (s, 3H), 6.7 (s, 1H), 7.07 (s, 1H), 7.36-7.62 (m, 3H), 7.85 (s, 1H), 8.13 (s, 1H), 8.71 (s, 1H) 10.8 (s, 1H), 11.95 (s, 1H); Mass Spectrum: $M+H^+$ 523 and 525.

The 4-amino-6-methoxy-7-[6-(2-methylimidazol-1-yl)-1-hexynyl]quinazoline used as a starting material was prepared as follows:

Using an analogous procedure to that described in the second last paragraph of Note [115] above, 6-(2-methylimidazol-1-yl)-1-hexyne was reacted with 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[6-(2-methylimidazol-1-yl)-1-hexynyl]quinazoline; NMR Spectrum: ($DMSOd_6$) 1.56 (m, 2H), 1.85 (m, 2H), 2.28 (s, 3H), 2.56 (m, 2H), 3.9 (m, 2H), 3.98 (s, 3H), 6.75 (br m, 1H), 7.1 (br m, 1H), 7.36-7.82 (m, 3H), 7.63 (s, 1H), 7.98 (s, 1H), 8.61 (s, 1H); Mass Spectrum: $M+H^+$ 509 and 511.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

6-(2-Methylimidazol-1-yl)-1-hexyne was obtained by the reaction of 6-mesyloxy-1-hexyne with 2-methylimidazole using an analogous procedure to that described in J. Heterocyclic Chemistry, 1994, 31, 1421.

[119] DMF was used as the reaction solvent and 4-dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.58 (m, 2H), 1.82 (m, 2H), 2.28 (s, 3H), 2.55 (m, 2H), 3.95 (m, 5H), 6.7 (s, 1H), 7.05 (s, 1H), 7.1-7.4 (m, 3H), 7.85 (s, 1H), 8.12 (s, 1H), 8.74 (s, 1H), 10.79 (s, 1H), 11.69 (s, 1H); Mass Spectrum: $M+H^+$ 491.

[120] DMF was used as the reaction solvent and 4-dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 2.28 (s, 6H), 3.54 (s, 2H), 3.98 (s, 3H), 7.18-7.47 (m, 3H), 7.92 (s, 1H), 8.15 (s, 1H), 8.74 (s, 1H), 10.8 (s, 1H), 11.68 (s, 1H); Mass Spectrum: $M+H^+$ 412.

The 4-amino-6-methoxy-7-(3-dimethylamino-1-propynyl)quinazoline used as a starting material was prepared as follows:

Using an analogous procedure to that described in the second last paragraph of Note [115] above, 3-dimethylamino-1-propyne was reacted with 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline to give 4-(2-bromo-

4-fluorophenoxy)-6-methoxy-7-(3-dimethylamino-1-propynyl)quinazoline; NMR Spectrum: ($DMSOd_6$) 2.29 (s, 6H), 3.55 (s, 2H), 4.0 (s, 3H), 7.38-7.83 (m, 3H), 7.67 (s, 1H), 8.05 (s, 1H), 8.63 (s, 1H); Mass Spectrum: $M+H^+$ 430 and 432.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[121] The product gave the following data: Mass Spectrum: $M+H^+$ 467.

[122] The product gave the following data: Mass Spectrum: $M+H^+$ 454.

[123] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42-1.56 (m, 2H), 1.84-2.06 (m, 5H), 2.3 (s, 3H), 2.86-2.99 (m, 2H), 3.92 (s, 3H), 4.04 (d, 2H), 7.02 (m, 1H), 7.22 (s, 1H), 7.28 (s, 1H), 7.36 (d, 1H), 8.44 (d, 1H), 8.64 (s, 1H), 8.76 (s, 1H), 13.12 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

[124] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42-1.58 (m, 2H), 1.84-2.06 (m, 5H), 2.3 (s, 3H), 2.58 (s, 3H), 2.86-2.96 (m, 2H), 3.86 (s, 3H), 4.04 (d, 2H), 7.22-7.28 (m, 2H), 7.36 (d, 1H), 7.92 (m, 1H), 8.6 (s, 1H), 8.76 (s, 1H), 9.06 (d, 1H), 12.62 (s, 1H); Mass Spectrum: $M+H^+$ 481.

[125] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42-1.56 (m, 2H), 1.84-2.04 (m, 5H), 2.3 (s, 3H), 2.84-2.94 (m, 2H), 3.94 (s, 3H), 4.06 (d, 2H), 7.1 (s, 1H), 7.76-7.36 (m, 2H), 7.56 (d, 1H), 8.22 (s, 1H), 8.78 (m, 2H), 13.16 (s, 1H); Mass Spectrum: $M+H^+$ 524 and 526.

[126] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42-1.56 (m, 2H), 1.86-2.06 (m, 5H), 2.3 (s, 3H), 2.84-2.96 (m, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.04 (d, 2H), 6.84 (d, 1H), 7.04 (m, 1H), 7.2 (s, 1H), 7.28 (s, 1H), 8.3-8.38 (m, 2H), 8.76 (s, 1H), 12.74 (s, 1H); Mass Spectrum: $M+H^+$ 486 and 488.

[127] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.44-1.56 (m, 2H), 1.86-2.06 (m, 5H), 2.3-2.34 (m, 6H), 2.84-2.96 (m, 2H), 3.86 (s, 3H), 3.98 (s, 3H), 4.04 (d, 2H), 6.82-6.9 (m, 2H), 7.24 (s, 1H), 7.36 (s, 1H), 8.06 (s, 1H), 8.76 (s, 1H), 8.9 (s, 1H), 12.64 (s, 1H); Mass Spectrum: $M+H^+$ 466.

[128] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4-1.54 (m, 2H), 1.84-2.04 (m, 5H), 2.3 (s, 3H), 2.44 (s, 3H), 2.84-2.96 (m, 2H), 3.8 (s, 3H), 4.04 (d, 2H), 7.04 (m, 1H), 7.16 (d, 1H), 7.26 (s, 1H), 7.38 (s, 1H), 8.1 (s, 1H), 8.7 (s, 1H), 9.08 (s, 1H), 12.46 (s, 1H); Mass Spectrum: $M+H^+$ 470 and 472.

[129] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42-1.56 (m, 2H), 1.84-2.04 (m, 5H), 2.3 (s, 3H), 2.44 (s, 3H), 2.86-2.96 (m, 2H), 3.86 (s, 3H), 4.04 (d, 2H), 6.8

(m, 1H), 7.18-7.22 (m, 1H), 7.24 (s, 1H), 7.28 (s, 1H), 7.96 (m, 1H), 8.58 (s, 1H), 8.72 (s, 1H), 12.4 (s, 1H); Mass Spectrum: $M+H^+$ 454.

[130] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42-1.56 (m, 2H), 1.84-2.04 (m, 5H), 2.28 (s, 3H), 2.34 (s, 3H), 2.86-2.96 (m, 2H), 3.86 (s, 3H), 4.04 (d, 2H), 6.88 (m, 1H), 7.22-7.32 (m, 3H), 8.12 (s, 1H), 8.76 (m, 2H), 12.78 (s, 1H); Mass Spectrum: $M+H^+$ 470 and 472.

[131] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.78-1.84 (m, 4H), 2.16 (m, 2H), 2.5-2.58 (m, 4H), 2.66 (t, 2H), 3.98 (s, 3H), 4.28 (t, 2H), 6.72-6.8 (m, 1H), 7.16-7.18 (m, 1H), 7.2 (s, 1H), 7.34 (s, 1H), 8.06-8.16 (m, 1H), 8.38 (s, 1H), 8.76 (s, 1H), 12.76 (s, 1H); Mass Spectrum: $M+H^+$ 458.

[132] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.78-1.84 (m, 4H), 2.16 (m, 2H), 2.48-2.58 (m, 4H), 2.66 (t, 2H), 3.96 (s, 3H), 4.28 (t, 2H), 7.02 (m, 1H), 7.14 (s, 1H), 7.32-7.4 (m, 2H), 8.3 (s, 1H), 8.46 (d, 1H), 8.78 (s, 1H), 13.06 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

[133] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.78-1.84 (m, 4H), 2.16 (m, 2H), 2.44 (s, 3H), 2.54-2.6 (m, 4H), 2.68 (t, 2H), 3.84 (s, 3H), 4.28 (t, 2H), 7.04 (m, 1H), 7.16 (d, 1H), 7.3 (s, 1H), 7.34 (s, 1H), 8.14 (d, 1H), 8.7 (s, 1H), 8.8 (s, 1H), 12.4 (s, 1H); Mass Spectrum: $M+H^+$ 470 and 472.

[134] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.78-1.84 (m, 4H), 2.16 (m, 2H), 2.44 (s, 3H), 2.5-2.6 (m, 4H), 2.66 (t, 2H), 3.86 (s, 3H), 4.28 (t, 2H), 6.72-6.8 (m, 1H), 7.16-7.2 (m, 2H), 7.34 (s, 1H), 7.96 (m, 1H), 8.46 (s, 1H), 8.72 (s, 1H), 12.4 (s, 1H); Mass Spectrum: $M+H^+$ 454.

[135] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.78-1.84 (m, 4H), 2.06-2.22 (m, 2H), 2.46-2.6 (m, 7H), 2.68 (t, 2H), 3.84 (s, 3H), 4.28 (t, 2H), 7.28 (m, 2H), 7.36 (d, 1H), 7.92 (d, 1H), 8.7 (s, 1H), 8.8 (s, 1H), 9.08 (s, 1H), 12.66 (s, 1H); Mass Spectrum: $M+H^+$ 481.

[136] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.78-1.84 (m, 4H), 2.14 (m, 2H), 2.3 (s, 3H), 2.5-2.6 (m, 4H), 2.64 (t, 2H), 3.84 (s, 3H), 4.28 (t, 2H), 6.88 (m, 1H), 7.28-7.36 (m, 3H), 8.14 (d, 1H), 8.78 (s, 1H), 8.88 (s, 1H), 12.9 (s, 1H); Mass Spectrum: $M+H^+$ 470 and 472.

[137] DMF was used as the reaction solvent. The product was obtained as a dihydrochloride salt and gave the following data: NMR Spectrum: ($DMSOd_6$) 1.6-1.7 (m, 2H), 1.82-1.96 (m,

2H), 2.58-2.62 (t, 2H), 2.8 (s, 3H), 3.3-3.9 (m, 10H), 4.02 (s, 3H), 7.4-7.6 (m, 3H), 7.95 (s, 1H), 8.21 (s, 1H), 8.8 (s, 1H), 11.6-12.0 (m, 2H); Mass Spectrum: $M+H^+$ 541 and 543.

The 4-amino-6-methoxy-7-[6-(N-methylpiperazin-1-yl)-1-hexynyl]quinazoline used as a starting material was prepared as follows:

Using an analogous procedure to that described in the second last paragraph of Note [115] above, 6-(N-methylpiperazin-1-yl)-1-hexyne was reacted with 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[6-(N-methylpiperazin-1-yl)-1-hexynyl]quinazoline; NMR Spectrum: ($DMSOd_6$) 1.55-1.65 (m, 4H), 2.16 (s, 3H), 2.3-2.45 (m, 10H), 2.5-2.6 (m, 2H), 4.0 (s, 3H), 7.4-7.8 (m, 3H), 7.65 (s, 1H), 7.98 (s, 1H), 8.6 (s,1H); Mass Spectrum: $M+H^+$ 527 and 529.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

6-(N-Methylpiperazin-1-yl)-1-hexyne was obtained by the reaction of 6-mesyloxy-1-hexyne with N-methylpiperazine using an analogous procedure to that described in J. Heterocyclic Chemistry, 1994, 31, 1421.

[138] The reactants were heated to 45°C for 20 hours. The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.24 (s, 3H), 2.34 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.58 (s, 3H), 5.3 (s, 2H), 7.06 (d, 1H), 7.18 (d, 1H), 7.3-7.52 (m, 7H), 8.64 (s, 1H), 9.4 (s, 1H), 11.87 (s, 1H); Mass Spectrum: $M+H^+$ 500.

The 3-(N,N-dimethylcarbamoyl)-2,6-dimethylphenylisocyanate used as a starting material was prepared as follows:

A solution of di-tert-butyl dicarbonate (0.081 g) in methylene chloride (1.6 ml) and a solution of 3-amino-N,N,2,4-tetramethylbenzamide (J. Chem. Soc., Perkin Trans. I, 1973, 1-4; 0.072 g) in methylene chloride (1.0 ml) were added in turn to a solution of 4-dimethylaminopyridine (0.004 g) in methylene chloride (0.4 ml). The resultant mixture was stirred at ambient temperature for 20 minutes. There was thus obtained a solution of 3-(N,N-dimethylcarbamoyl)-2,6-dimethylphenylisocyanate which was used without further purification.

[139] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 0.37 (m, 2H), 0.62 (m, 2H), 1.32 (m, 1H), 2.25 (s, 6H), 3.94 (s, 3H), 4.03 (d, 2H), 7.12 (s, 3H), 7.22 (s, 1H), 8.07 (s, 1H), 8.66 (s, 1H), 10.38 (s, 1H), 11.68 (s, 1H); Mass Spectrum: $M+H^+$ 393.

The 4-amino-7-cyclopropylmethoxy-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (6.99 g), cyclopropylmethyl chloride (2.16 g), potassium iodide (0.043 g), potassium carbonate (12 g) and DMF (200 ml) was stirred and heated to 45°C for 16 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(4-bromo-2-fluorophenoxy)-7-cyclopropylmethoxy-6-methoxyquinazoline (7.6 g); NMR Spectrum: ($DMSOd_6$) 0.43 (m, 2H), 0.68 (m, 2H), 1.37 (m, 1H), 4.0 (s, 3H), 4.1 (d, 2H), 7.4 (s, 1H), 7.45 (m, 1H), 7.57 (m, 2H), 7.82 (m, 1H), 8.58 (s, 1H); Mass Spectrum: $M+H^+$ 421 and 423.

Using an analogous procedure to that described in the last paragraph of the portion of Example 1 that is concerned with starting materials, 4-(4-bromo-2-fluorophenoxy)-7-cyclopropylmethoxy-6-methoxyquinazoline (1.75 g) was reacted with ammonia in isopropanol. There was thus obtained 4-amino-7-cyclopropylmethoxy-6-methoxyquinazoline (1.75 g); NMR Spectrum: ($DMSOd_6$) 0.36 (m, 2H), 0.58 (m, 2H), 1.3 (m, 1H), 3.88 (s, 3H), 3.94 (d, 2H), 6.97 (s, 1H), 7.39 (br s, 2H), 7.55 (s, 1H), 8.25 (s, 1H); Mass Spectrum: $M+H^+$ 246.

[140] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.23-1.46 (m, 6H), 1.55-1.69 (m, 2H), 2.1 (s, 3H), 2.1-2.4 (m, 10H), 2.7-2.8 (m, 2H), 3.97 (s, 3H), 7.3-7.6 (m, 3H), 7.65 (s, 1H), 8.05 (s, 1H), 8.7 (s, 1H), 10.7 (s, 1H), 12.05 (s, 1H); Mass Spectrum: $M+H^+$ 545 and 547.

The 4-amino-6-methoxy-7-[6-(N-methylpiperazin-1-yl)hexyl]quinazoline used as a starting material was prepared as follows :-

A mixture of 4-amino-6-methoxy-7-[6-(N-methylpiperazin-1-yl)-1-hexynyl]quinazoline (0.145 g), 10% palladium-on-charcoal catalyst (0.02 g) and ethanol (10 ml) was stirred at ambient temperature under 5 atmospheres pressure of hydrogen until uptake of hydrogen ceased. The reaction mixture was filtered and the filtrate was evaporated. There was thus obtained the title compound as a solid (0.142 g); Mass Spectrum: $M+H^+$ 358.

[141] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.8-2.0 (m, 6H), 2.5-2.7 (m, 6H), 2.79-2.85 (t, 2H), 3.6 (s, 3H), 7.2-7.4 (m, 3H), 7.4 (s, 1H), 7.73 (s, 1H), 8.72 (s, 1H), 9.3-9.45 (s, 1H), 12.3 (s, 1H); Mass Spectrum: $M+H^+$ 474 and 476.

The 4-amino-6-methoxy-7-[3-(pyrrolidin-1-yl)propyl]quinazoline used as a starting material was prepared by the hydrogenation of 4-amino-6-methoxy-7-[3-(pyrrolidin-1-yl)-1-propynyl]quinazoline using an analogous procedure to that described in Note [139] above.

[142] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.6-1.75 (m, 2H), 2.1 (s, 3H), 2.2-2.4 (m, 10H), 3.3 (m, 2H), 4.0 (s, 3H), 7.25-7.6 (m, 3H), 7.94 (s, 1H), 8.19 (s, 1H), 8.5 (br t, 1H), 8.77 (s, 1H), 10.87 (s, 1H), 11.96 (s, 1H); Mass Spectrum: $M+H^+$ 546 and 548.

The 4-amino-6-methoxy-7-{N-[3-(N-methylpiperazin-1-yl)propyl]carbamoyl}quinazoline used as a starting material was prepared as follows :-

A mixture of 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline (9.7 g), palladium acetate (0.137 g), 1,3-bis(diphenylphosphino)propane (0.402 g), triethylamine (5.5 ml), DMF (60 ml) and methanol (1.2L) was stirred and heated to 70°C under 10 atmospheres pressure of carbon monoxide for 2 hours. The reaction mixture was cooled to ambient temperature and the solid was isolated, washed with methanol and dried under vacuum. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-methoxycarbonylquinazoline (5.96 g); NMR Spectrum: ($DMSOd_6$) 3.91 (s, 3H), 4.02 (s, 3H), 7.4-7.8 (m, 3H), 7.8 (s, 1H), 8.2 (s, 1H), 8.69 (s, 1H); Mass Spectrum: $M+H^+$ 407 & 409.

A mixture of a portion (2 g) of the product so obtained, 2,4,6-trimethoxybenzylamine hydrochloride (2.34 g), anhydrous potassium carbonate (2.76 g) and DMF (20 ml) was stirred and heated to 70°C for 2 hours. The mixture was cooledto ambient temperature and diluted with water. The resultant solid was isolated, washed in turn with water and diethyl ether and dried under vacuum at 80°C. There was thus obtained 6-methoxy-7-methoxycarbonyl-4-(2,4,6-trimethoxybenzylamino)quinazoline (1.9 g); NMR Spectrum: ($DMSOd_6$) 3.75-3.85 (m, 15H), 4.55 (d, 2H), 6.3 (s, 2H), 7.8 (m, 2H), 7.9 (m, 1H), 8.45 (s, 1H); Mass Spectrum: $M+H^+$ 414.

A portion (1.8 g) of the material so obtained was suspended in a mixture of THF (27 ml), methanol (14 ml) and water (14 ml) and lithium hydroxide (0.945 g) was added portionwise. The resultant mixture was stirred at ambient temperature for 2 hours. The mixture was concentrated by evaporation and acidified to pH4 by the addition of 2N aqueous hydrochloride acid. The resultant solid was isolated, washed in turn with water and diethyl ether and dried at 80°C. There was thus obtained 7-carboxy-6-methoxy-4-(2,4,6-trimethoxybenzylamino)quinazoline (1.68 g); NMR Spectrum: ($DMSOd_6$) 3.7-3.9

(m, 12H), 4.55 (s, 2H), 6.28 (s, 2H), 7.7-7.9 (m, 3H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 400.

A mixture of a portion (0.3 g) of the material so obtained, 3-(N-methylpiperazin-1-yl)propylamine (0.33 g), N-hydroxybenzotriazole (0.13 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.287 g) and DMF (3 ml) was stirred at ambient temperature for 16 hours. Dilute aqueous potassium carbonate solution was added and the resultant solid was isolated, washed in turn with water and diethyl ether and dried at 60°C under vacuum. There was thus obtained 6-methoxy-7-{N-[3-(N-methylpiperazin-1-yl)propyl]carbamoyl}-4-(2,4,6-trimethoxybenzylamino)quinazoline (0.285 g); NMR Spectrum: ($DMSOd_6$) 1.58-1.7 (m, 2H), 2.11 (s, 3H), 2.2-2.4 (m, 10H), 3.2-3.4 (m, 2H), 3.7-3.92 (m, 12H), 4.51 (m, 2H), 6.3 (s, 2H), 7.7-7.86 (m, 3H), 8.3-8.4 (br t, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 539.

A mixture of the material so obtained, trifluoroacetic acid (2 ml), anisole (0.2 ml) and concentrated sulphuric acid (0.2 ml) was stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was partitioned between diethyl ether and a 2M aqueous potassium carbonate solution. The aqueous solution was evaporated and the residue was extracted with methanol. The methanolic extracts were evaporated and the resultant solid was dried under vacuum. There was thus obtained 4-amino-6-methoxy-7-{N-[3-(N-methylpiperazin-1-yl)propyl]carbamoyl}quinazoline (0.086 g), Mass Spectrum: $M+H^+$ 359.

[143] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.88-2.02 (m, 2H), 3.18-3.25 (m, 2H), 4.0 (s, 3H), 4.0-4.08 (m, 2H), 6.88 (s, 1H), 7.22 (s, 1H), 7.3-7.6 (m, 4H), 7.98 (s, 1H), 8.22 (s, 1H), 8.55-8.6 (br t, 1H), 8.8 (s, 1H), 10.9 (s, 1H), 11.98 (s, 1H); Mass Spectrum: $M+H^+$ 514 and 516.

The 4-amino-6-methoxy-7-{N-[3-(N-methylpiperazin-1-yl)propyl]carbamoyl}quinazoline used as a starting material was prepared by the reaction of 7-carboxy-6-methoxy-4-(2,4,6-trimethoxybenzylamino)quinazoline and 3-(1-imidazolyl)propylamine and subsequent cleavage of the 2,4,6-trimethoxybenzyl group using analogous procedures to those described in Note [142] above.

[144] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 3.18-3.24 (m, 4H), 3.3-3.4 (m, 4H), 3.97 (s, 3H), 7.18 (s, 1H), 7.3-7.6 (m, 3H), 7.98 (s, 1H), 8.65 (s, 1H), 10.6 (s, 1H), 12.12 (s, 1H); Mass Spectrum: $M+H^+$ 461 and 463.

The 4-amino-6-methoxy-7-(N-methylpiperazin-1-yl)quinazoline used as a starting material was prepared as follows :-

A mixture of 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline (0.8 g), 1-methylpiperazine (0.35 ml), caesium carbonate (0.78g), 1,1'-bis(diphenylphosphino)ferrocene (0.088 g), bis(dibenzylideneacetone)palladium (0.046 g) and toluene (12 ml) was stirred and heated to 100°C for 6 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic extract was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(N-methylpiperazin-1-yl)quinazoline (0.26 g); NMR Spectrum: ($CDCl_3$) 2.4 (s, 3H), 2.66-2.68 (m, 4H), 3.34-3.38 (m, 4H), 4.05 (s, 3H), 7.1-7.44 (m, 3H), 7.38 (s, 1H), 7.55 (s, 1H), 8.58 (s, 1H); Mass Spectrum: $M+H^+$ 447 and 449.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[145] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.43 (s, 9H), 3.13-3.19 (m, 4H), 3.45-3.55 (m, 4H), 4.0 (s, 3H), 7.2 (s, 1H), 7.35-7.6 (m, 3H), 8.02 (s, 1H), 8.65 (s, 1H), 10.65 (s, 1H), 12.1 (s, 1H); Mass Spectrum: $M+H^+$ 547 and 549.

The 4-amino-7-[N-(tert-butoxycarbonyl)piperazin-1-yl]-6-methoxyquinazoline used as a starting material was prepared from as follows :-

The procedure described in the first paragraph of the portion of Note [144] above which is concerned with the preparation of starting materials was repeated except that 1-(tert-butoxycarbonyl)piperazine was used in place of 1-methylpiperazine. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[N-(tert-butoxycarbonyl)piperazin-1-yl]quinazoline; NMR Spectrum: ($CDCl_3$) 1.5 (s, 9H), 3.22 (m, 4H), 3.66 (m, 4H), 4.08 (s, 3H), 7.1-7.46 (m, 3H), 7.35 (s, 1H), 7.57 (s, 1H), 8.58 (s, 1H); Mass Spectrum: $M+H^+$ 533 and 535.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[146] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.75-1.85 (m, 2H), 2.3-2.45 (m, 6H), 3.25-3.35 (m, 2H), 3.6-3.68 (m, 4H), 4.0 (s, 3H), 6.7 (s, 1H), 6.89 (t, 1H),

7.35-7.6 (m, 3H), 7.88 (s, 1H), 8.51 (s, 1H), 10.3 (s, 1H), 12.25 (s, 1H); Mass Spectrum: $M+H^+$ 505 and 507.

The 4-amino-6-methoxy-7-(3-morpholinopropylamino)quinazoline used as a starting material was prepared from as follows :-

The procedure described in the first paragraph of the portion of Note [144] above which is concerned with the preparation of starting materials was repeated except that 3-morpholinopropylamine was used in place of 1-methylpiperazine. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-(3-morpholinopropylamino)quinazoline; NMR Spectrum: ($CDCl_3$) 1.9-2.0 (m, 2H), 2.48-2.6 (m, 6H), 3.35-3.42 (m, 2H), 3.78-3.82 (m, 4H), 4.07 (s, 3H), 6.4-6-48 (t, 1H), 6.86 (s, 1H), 7.1-7.42 (m, 3H), 7.43 (s, 1H), 8.5 (s, 1H); Mass Spectrum: $M+H^+$ 491 and 493.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[147] The product gave the following data: NMR Spectrum: ($DMSOd_6$) 2.0-2.12 (m, 2H), 3.15-3.25 (m, 2H), 4.0 (s, 3H), 4.05-4.12 (m, 2H), 6.45-6.5 (t, 1H), 6.68 (s, 1H), 6.9 (s, 1H), 7.22 (s, 1H), 7.35-7.6 (m, 3H), 7.65 (s, 1H), 7.88 (s, 1H), 8.55 (s, 1H), 10.35 (s, 1H), 12.22 (s, 1H); Mass Spectrum: $M+H^+$ 486 and 488.

The 4-amino-7-(3-imidazol-1-ylpropylamino)-6-methoxyquinazoline used as a starting material was prepared from as follows :-

The procedure described in the first paragraph of the portion of Note [144] above which is concerned with the preparation of starting materials was repeated except that 3-imidazol-1-ylpropylamine was used in place of 1-methylpiperazine. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-7-(3-imidazol-1-ylpropylamino)-6-methoxyquinazoline; NMR Spectrum: ($CDCl_3$) 2.2-2.3 (m, 2H), 3.3-3.4 (m, 2H), 4.05 (s, 3H), 4.1-4.15 (m, 2H), 5.04-5.13 (br t, 1H), 6.88 (s, 1H), 6.96 (s, 1H), 7.1 (s, 1H), 7.15-7.5 (m, 3H), 7.45 (s, 1H), 7.52 (s, 1H), 8.55 (s, 1H); Mass Spectrum: $M+H^+$ 472 and 474.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[148] The reactants were heated to 45°C for 20 hours. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.2-1.4 (m, 2H), 1.66-1.94 (m, 5H), 2.14 (s, 3H), 2.16 (s, 3H), 2.26 (s, 3H), 2.7 (m, 2H), 2.78 (s, 3H), 2.98 (s, 3H), 3.94 (s, 3H), 4.04 (d, 2H), 7.0 (d, 1H), 7.18 (d, 1H), 7.24 (s, 1H), 8.02 (s, 1H), 8.64 (s, 1H), 10.36 (s, 1H), 11.72 (s, 1H); Mass Spectrum: $M+H^+$ 521.

[149] The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.73 (m, 4H), 2.09 (m, 2H), 2.28 (s, 3H), 2.48 (br m, 4H), 2.57 (t, 2H), 3.35 (s, 3H), 4.18 (t, 2H), 5.24 (s, 1H), 7.08 (d, 2H), 7.19 (s, 1H), 7.27 (t, 1H), 7.42 (s, 1H), 8.61 (s, 1H), 9.72 (s, 1H), 12.19 (s, 1H); Mass Spectrum: $M+H^+$ 470 and 472.

[150] The product gave the following data: Mass Spectrum: $M+H^+$ 450 and 452.

The 4-amino-7-(3-methoxypropylamino)-6-methoxyquinazoline used as a starting material was prepared from as follows :-

The procedure described in the first paragraph of the portion of Note [144] above which is concerned with the preparation of starting materials was repeated except that 3-methoxypropylamine was used in place of 1-methylpiperazine. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-7-(3-methoxypropylamino)-6-methoxyquinazoline.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[151] The product gave the following data: Mass Spectrum: $M+H^+$ 421 and 423.

The 4-amino-7-(2-aminoethylamino)-6-methoxyquinazoline used as a starting material was prepared from as follows :-

The procedure described in the first paragraph of the portion of Note [144] above which is concerned with the preparation of starting materials was repeated except that ethylenediamine was used in place of 1-methylpiperazine. There was thus obtained 7-(2-aminoethylamino)-4-(2-bromo-4-fluorophenoxy)-6-methoxyquinazoline.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

[152] The product gave the following data: Mass Spectrum: $M+H^+$ 491 and 493.

The 4-amino-7-[N-(2-diethylaminoethyl)-N-methylamino]-6-methoxyquinazoline used as a starting material was prepared from as follows :-

The procedure described in the first paragraph of the portion of Note [144] above which is concerned with the preparation of starting materials was repeated except that N-(2-diethylaminoethyl)-N-methylamine was used in place of 1-methylpiperazine. There was thus obtained 4-(2-bromo-4-fluorophenoxy)-7-[N-(2-diethylaminoethyl)-N-methylamino]-6-methoxyquinazoline.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] above to give the required starting material.

Example 3 **1-(7-benzyloxy-6-methoxyquinazolin-4-yl)-3-(2,6-dichlorophenyl)urea**

2,6-Dichlorophenyl isocyanate (0.745 g) was added to a solution of 4-amino-7-benzyloxy-6-methoxyquinazoline (0.279 g) in chloroform (10 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The resultant precipitate was isolated by filtration. There was thus obtained the title compound (0.343 g); NMR Spectrum: ($DMSOd_6$) 3.96 (s, 3H), 5,32 (s, 2H), 7.35–7.60 (m, 10H), 8.1 (s, 1H), 8.69 (s, 1H), 10.65 (s, 1H), 12.09 (s, 1H); Mass Spectrum: $M+H^+$ 467 & 469.

Example 4 **1-(2,6-dichlorophenyl)-3-(6,7-dimethoxyquinazolin-4-yl)urea**

Using an analogous procedure to that described in Example 3, 2,6-dichlorophenyl isocyanate was reacted with 4-amino-6,7-dimethoxyquinazoline (European Patent Application No. 30156, Chemical Abstract volume 95, abstract 187290) to give the title compound; NMR Spectrum: ($DMSOd_6$) 3.96 (s, 3H), 7.31 (m, 2H), 7.38 (t, 1H), 7.5 (d, 2H), 7.6 (d, 2H), 8.43 (s, 1H), 8.7 (s, 1H), 10.61 (s, 1H), 12.09 (s, 1H); Mass Spectrum: $M+H^+$ 393 & 395.

Example 5 **1-(2,6-dichlorophenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-methylurea**

6-Methoxy-4-methylamino-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (0.195 g) was added to 2,6-dichlorophenyl isocyanate (0.3 g) under argon and the solids were mixed together using a spatula. The mixture was heated to 85°C with gentle mixing for 40 minutes. The mixture was cooled to ambient temperature, dissolved in a mixture of chloroform (15 ml) and methanol (5 ml) and purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 1% aqueous ammonium hydroxide solution as eluent. There was thus obtained the title compound (0.016 g); NMR Spectrum: ($CDCl_3$) 1.5 (m, 2H), 1.98 (m, 5H), 2.3 (s, 3H), 2.91 (d, 2H), 3.6 (s, 3H), 4.02 (s, 3H), 4.03 (d, 2H), 7.1 (t, 1H), 7.28 (s, 2H), 7.37 (d, 2H), 8.61 (s, 1H), 8.96 (s, 1H); Mass Spectrum: $M+H^+$ 504.

The 6-methoxy-4-methylamino-7-(N-methylpiperidin-4-ylmethoxy)quinazoline used as a starting material was obtained as follows :-

A mixture of 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (1 g) and methylamine (1M solution in THF; 20 ml) was heated with agitation in a Carius tube at 120°C for 16 hours. The Carius tube was cooled and opened and the reaction mixture was evaporated. The residue was partitioned between chloroform and a 2N aqueous sodium

hydroxide solution. The chloroform solution was dried over magnesium sulphate and evaporated and the resultant solid was washed with methyl tert-butyl ether (20 ml). There was thus obtained the required starting material (0.48 g); NMR Spectrum: ($DMSOd_6$) 1.33 (m, 2H), 1.8 (m, 5H), 2.14 (s, 3H), 2.76 (d, 2H), 2.96 (d, 3H), 3.85 (s, 3H), 3.92 (d, 2H), 7.03 (s, 1H), 7.51 (s, 1H), 7.84 (q, 1H), 8.31 (s, 1H).

Example 6 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-(2-methylbenzyl)urea

Using an analogous procedure to that described in Example 3, 2-methylbenzyl isocyanate was reacted with 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline. The resultant solid was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride, methanol and a 1% aqueous ammonium hydroxide solution as eluent. There was thus obtained the title compound; NMR Spectrum: ($CDCl_3$) 1.39–1.56 (m, 2H), 1.84–2.04 (m, 5H), 2.29 (s, 3H), 2.39 (s, 3H), 2.9 (d, 2H), 3.92 (s, 3H), 4.03 (d, 2H), 4.66 (d, 2H), 7.21 (m, 4H), 7.34 (m, 2H), 8.6 (s, 1H), 8.74 (s, 1H), 10.44 (t, 1H); Mass Spectrum: $M+H^+$ 450.

Example 7 1-(2,6-dichlorophenyl)-3-(thieno[3,2-*d*]pyrimidin-4-yl)urea

2,6-Dichlorophenyl isocyanate (0.075 g) was added to a mixture of 4-aminothieno[3,2-*d*]pyrimidine (Tetrahedron, 1971, 27, 487; 0.201 g) and acetonitrile (16 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated and washed in turn with diethyl ether and methanol. There was thus obtained the title compound (0.31 g); NMR Spectrum: ($DMSOd_6$) 7.25 (t, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.95 (d, 1H), 8.4 (s, 1H), 8.8 (s, 1H), 11.7 (br s, 1H); Mass Spectrum: $M+H^+$ 339 and 341; Elemental Analysis: Found C, 45.8; H, 2.4; N, 16.5; $C_{13}H_8Cl_2N_4OS$ requires C, 46.03; H, 2.38; N, 16.52 %.

Example 8 (*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}acrylic acid

Hydrogen chloride gas was bubbled during 3 hours through a stirred solution of tert-butyl (*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}acrylate (1.4 g) in methylene chloride (200 ml) which had been cooled in an ice-bath to 0°C. The mixture was evaporated and there was thus obtained the title compound as its hydrochloride salt;

(1.3 g); NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 6.6 (d, 1H, J = 16Hz), 7.4 (t, 1H), 7.65 (d, 2H), 7.95 (d, 1H), 7.96 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 409, 411 and 413.

The tert-butyl (*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}acrylate used as a starting material was obtained as follows :-

A mixture of methyl 3-aminothiophene-2-carboxylate (94 g), formamidine acetic acid salt (187 g) and 2-hydroxyethyl methyl ether (1 L) was stirred and heated to reflux for 3 hours. The mixture was cooled to ambient temperature and water (400 ml) was added. The resultant solid was isolated, washed thoroughly with water and with diethyl ether and dried under vacuum. There was thus obtained 3,4-dihydrothieno[3,2-*d*]pyrimidin-4-one (65 g); NMR Spectrum: ($DMSOd_6$) 7.4 (d, 1H), 8.15 (s, 1H), 8.18 (d, 2H); Mass Spectrum : $M+Na^+$ 175.

A mixture of a portion (20 g) of the material so obtained, thionyl chloride (250 ml) and DMF (1 ml) was heated to reflux for 2 hours. The mixture was evaporated. Toluene was added and the mixture was evaporated. The residual solid was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The solid so obtained was triturated under petroleum ether (b.p. 60-80°C), re-isolated and dried under vacuum. There was thus obtained 4-chlorothieno[3,2-*d*]pyrimidine (18.5 g); NMR Spectrum: ($CDCl_3$) 7.65 (d, 1H), 8.1 (d, 1H), 9.0 (s, 1H); Mass Spectrum: M^+ 170 and 172.

A portion (17 g) of the material so obtained was dissolved in DMF (100 ml). Sodium methylthiolate (9.1 g) was added and the mixture was stirred at ambient temperature for 1.5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulphate and purified by column chromatography on silica using a 9:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-methylthiothieno[3,2-*d*]pyrimidine (16.5 g); NMR Spectrum: ($CDCl_3$) 2.76 (s, 3H), 7.5 (d, 1H), 7.85 (d, 1H), 8.97 (s, 1H).

A portion (5.5 g) of the material so obtained was dissolved in THF (20 ml) and cooled to -78°C. A solution of lithium diisopropylamide [prepared using diisopropylamine (10.5 ml) and n-butyllithium (2.5M in THF; 30 ml)] was added and the mixture was stirred at -78°C for 1 hour. DMF (7 ml) was added and the mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The resultant mixture was partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic layer was evaporated and the residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 6-formyl-

4-methylthiothieno[3,2-*d*]pyrimidine (4.1 g); NMR Spectrum: ($CDCl_3$) 2.78 (s, 3H), 8.13 (s, 1H), 9.04 (s, 1H), 10.23 (s, 1H); Mass Spectrum : $M+H^+$ 211.

tert-Butoxycarbonylmethylenetriphenylphosphorane (20.6 g) was added portionwise to a solution of 6-formyl-4-methylthiothieno[3,2-*d*]pyrimidine (9.6 g) in methylene chloride (500 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was concentrated to half of its original volume and poured onto a column of silica. The column was eluted initially with methylene chloride followed by a 19:1 mixture of methylene chloride and ethyl acetate. The material so obtained was triturated under petroleum ether (b.p. 60-80°C), re-isolated and dried under vacuum. There was thus obtained tert-butyl (*E*)-3-(4-methylthiothieno[3,2-*d*]pyrimidin-6-yl)acrylate (12 g); NMR Spectrum: ($CDCl_3$) 1.54 (s, 9H), 2.76 (s, 3H), 6.42 (d, 1H, J = 15 Hz), 7.53 (s, 1H), 7.8 (d, 1H), 8.94 (s, 1H); Mass Spectrum: $M+H^+$ 308.

A portion (2.9 g) of the material so obtained was dissolved in methylene chloride (200 ml) and m-chloroperoxybenzoic acid (70% ; 9.25 g) was added. The resultant mixture was stirred at ambient temperature for 2 hours. The mixture was washed with an aqueous sodium bisulphite solution. The organic layer was washed with a dilute (5%) aqueous sodium bicarbonate solution and with brine, dried over magnesium sulphate and evaporated. There was thus obtained tert-butyl (*E*)-3-(4-methylsulphonylthieno[3,2-*d*]pyrimidin-6-yl)acrylate (3.1 g); NMR Spectrum: ($CDCl_3$) 1.55 (s, 9H), 3.39 (s, 3H), 6.6 (d, 1H, J = 16 Hz), 7.71 (s, 1H), 7.85 (d, 1H), 9.3 (s,1H).

A solution of the sulphone so obtained (3 g) in THF (100 ml) was cooled at 0°C and gaseous ammonia was bubbled through the solution for 2 hours. The mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and methanol as eluent. There was thus obtained tert-butyl (*E*)-3-(4-aminothieno[3,2-*d*]pyrimidin-6-yl)acrylate (1.7 g); NMR Spectrum: ($CDCl_3$) 1.55 (s, 9H), 5.25 (br s, 2H), 6.38 (d, 1H, J = 16 Hz), 7.51 (s, 1H), 7.76 (d, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 277.

A mixture of the material so obtained, 2,6-dichlorophenyl isocyanate (1.41 g) and methylene chloride (250 ml) was stirred at ambient temperature for 3 hours. Water was added and the organic layer was separated, washed with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and methanol as eluent. There was thus obtained tert-butyl (*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}acrylate

(1.5 g); NMR Spectrum: ($CDCl_3$) 1.57 (s, 9H), 6.29 (d, 1H, J = 16 Hz), 7.3 (t, 1H), 7.53 (d, 2H), 7.55 (s, 1H), 7.74 (d, 1H), 8.8 (s, 1H), 9.95 (br s, 1H), 11.8 (br s, 1H); Mass Spectrum: $M+H^+$ 465, 467 & 469.

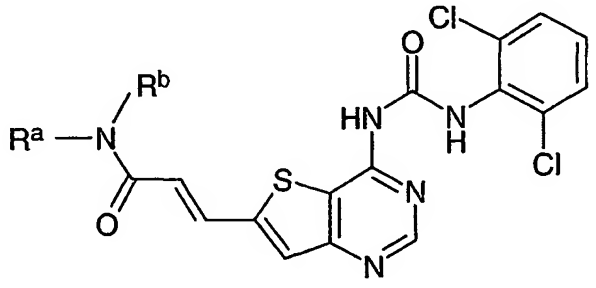
Example 9 **(*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}-N-(2-piperidinoethyl)acrylamide**

Diphenylphosphoryl azide (0.085 ml) was added to a mixture of (*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}acrylic acid hydrochloride salt (0.11 g), 2-piperidinoethylamine (0.064 g), triethylamine (0.07 ml) and DMF (1.5 ml). The mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether, isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.087 g); NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.3-1.5 (m, 1H), 1.6-1.8 (m, 4H), 1.85 (d, 2H), 2.95 (t, 2H), 3.2 (t, 2H), 3.55 (d, 2H), 3.6 (t, 2H), 6.82 (d, 1H, J = 16 Hz), 7.4 (t, 1H), 7.6 (d, 1H), 7.86 (s, 1H), 7.86 (d, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 519 and 521.

Example 10

Using an analogous procedure to that described in Example 9, the appropriate amine was reacted with (*E*)-3-{4-[3-(2,6-dichlorophenyl)ureido]thieno[3,2-*d*]pyrimidin-6-yl}acrylic acid to give the compounds described in Table II.

Table II



No.	R^a	R^b	Note
1	2-dimethylaminoethyl	hydrogen	(a)

2	3-dimethylaminopropyl	hydrogen	(b)
3	2-pyrrolidin-1-ylethyl	hydrogen	(c)
4	3-(2-oxopyrrolidin-1-yl)propyl	hydrogen	(d)
5	3-morpholinopropyl	hydrogen	(e)
6	3-(4-methylpiperazin-1-yl)propyl	hydrogen	(f)
7	3-imidazol-1-ylpropyl	hydrogen	(g)
8	4-pyridylmethyl	hydrogen	(h)
9	2-(2-pyridyl)ethyl	hydrogen	(i)
10	2-(2-pyridyl)ethyl	methyl	(j)

Notes

(a) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 2.9 (s, 6H), 3.25 (t, 2H), 3.6 (t, 2H), 6.9 (d, 1H, J = 16 Hz), 7.42 (t, 1H), 7.65 (d, 2H), 7.85 (d, 1H), 7.88 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 479 and 481.

(b) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.8-1.9 (m, 2H), 2.81 (s, 3H), 3.15 (m, 2H), 3.3 (t, 2H), 6.84 (d, 1H, J = 19 Hz), 7.45 (t, 1H), 7.6 (d, 2H), 7.81 (d, 1H), 7.85 (s, 1H), 9.02 (s, 1H); Mass Spectrum: $M+H^+$ 493 and 495.

(c) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.8-1.95 (m, 2H), 1.95-2.1 (m, 2H), 3.0-3.15 (m, 2H), 3.3 (t, 2H), 3.55 (t, 2H), 3.55-3.7 (m, 2H), 6.8 (d, 1H), 7.42 (t, 1H), 7.6 (d, 2H), 7.82 (d, 1H), 7.84 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 505 and 507.

(d) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.65-1.75 (m, 2H), 1.9-2.0 (m, 2H), 2.3 (t, 2H), 3.25 (t, 2H), 3.3 (t, 2H), 3.4 (t, 2H), 6.25 (d, 1H, J = 16 Hz), 7.42 (t, 1H), 7.62 (d, 2H), 7.81 (d, 1H), 7.85 (s, 1H), 9.12 (s, 1H); Mass Spectrum: $M+H^+$ 533 and 535.

(e) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.85-2.0 (m, 2H), 3.0-3.25 (m, 4H), 3.3 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 4.0 (d, 2H), 6.9 (d, 1H, J = 16 Hz), 7.45 (t, 1H), 7.61 (d, 2H), 7.85 (d, 1H), 7.87 (s, 1H), 9.08 (s, 1H); Mass Spectrum: $M+H^+$ 535 and 537.

(f) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 1.85-2.0 (m, 2H), 2.95 (s, 3H), 3.2-3.4 (m, 6H), 3.4-4.0 (br m, 6H), 6.85 (d, 1H, J = 14 Hz),

7.42 (t, 1H), 7.65 (d, 2H), 7.82 (d, 1H), 7.85 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 548 and 550.

(g) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 2.0-2.1 (m, 2H), 3.25 (t, 2H), 4.25 (t, 2H), 6.75 (d, 1H, J = 15 Hz), 7.2-7.3 (d, 1H), 7.4 (t, 2H), 7.6 (d, 2H), 7.85 (m, 2H), 8.9 (s, 1H), 9.2 (s, 1H); Mass Spectrum: $M+H^+$ 516.

(h) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 4.75 (br s, 2H), 6.95 (d, 1H, J = 15 Hz), 7.4 (t, 1H), 7.6 (d, 1H), 7.85 (s, 1H), 7.87 (d, 1H), 8.05 (d, 2H), 8.9 (d, 2H), 8.93 (s, 1H); Mass Spectrum: $M+H^+$ 499 and 501.

(i) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 3.25 (t, 2H), 3.7 (t, 2H), 6.8 (d, 1H, J = 15 Hz), 7.42 (t, 1H), 7.62 (d, 2H), 7.75 (d, 1H), 7.83 (s, 1H), 8.0 (t, 1H), 8.05 (d, 1H), 8.58 (t, 1H), 8.9 (d, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 513 and 515.

(j) The product gave the following data: NMR Spectrum: ($DMSOd_6$ and CF_3COOD) 3.4 (s, 3H), 5.0 (s, 2H), 7.35-7.5 (m, 2H), 7.61 (d, 2H), 7.8 (d, 1H), 7.98 (s, 1H), 7.85-8.1 (m, 2H), 8.6 (t, 1H), 8.9 (d, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 513 and 515.

Example 11 1-benzyl-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]urea

Using an analogous procedure to that described in Example 1 except that the reaction mixture was heated to 35°C for 16 hours, benzyl isocyanate was reacted with 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline to give the title compound; NMR Spectrum: ($DMSOd_6$): 1.3-1.5 (m, 2H), 1.8-1.9 (m, 4H), 1.95 (t, 1H), 2.2 (s, 3H), 2.8 (br d, 2H), 3.9 (br s, 3H), 4.0 (br d, 2H), 4.5 (br d, 2H), 7.2-7.3 (m, 2H), 7.3-7.4 (m, 4H), 8.0 (br s, 1H), 8.55 (br s, 1H), 10.2-10.5 (br s, 1H), 10.4 (t, 1H); Mass Spectrum: $M+H^+$ 436.

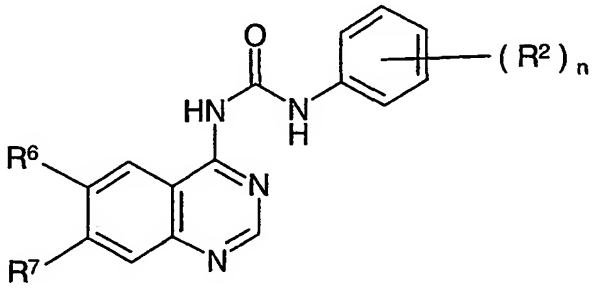
Example 12 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-phenethylurea

Using an analogous procedure to that described in Example 3, phenethyl isocyanate was reacted with 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline to give the title compound; NMR Spectrum: ($CDCl_3$) 1.48 (m, 2H), 1.98 (m, 5H), 2.29 (s, 3H), 2.91 (m, 4H), 3.7 (q, 2H), 4.02 (d, 5H), 7.28 (m, partially obscured by $CHCl_3$ peak), 8.47 (s, 1H), 8.65 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 450.

Example 13

Using an analogous procedure to that described in Example 1 except that, unless otherwise stated, chloroform was used in place of methylene chloride as the reaction solvent, the appropriate 4-aminoquinazoline was reacted with the appropriate isocyanate to give the compounds described in Table III.

Table III



No.	R^6	R^7	$(R^2)_n$	Note
1	methoxy	N-methylpiperidin-4-ylmethoxy	4-chloro	(a)
2	methoxy	N-methylpiperidin-4-ylmethoxy	3,4-dichloro	(b)
3	methoxy	N-methylpiperidin-4-ylmethoxy	3,5-dichloro	(c)
4	methoxy	N-methylpiperidin-4-ylmethoxy	4-bromo	(d)
5	methoxy	N-methylpiperidin-4-ylmethoxy	4-nitro	(e)

Notes

(a) DMF was used in place of methylene chloride as the reaction solvent. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.48 (m, 2H), 1.97 (m, 5H), 2.29 (s, 3H), 2.91 (m, 2H), 3.81 (s, 3H), 4.04 (d, 2H), 7.25 (s, 2H), 7.3 (d, 2H), 7.57 (d, 2H), 8.73 (s, 1H), 8.91 (s, 1H), 12.5 (s, 1H); Mass Spectrum: $M+H^+$ 456 and 458.

(b) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.51 (m, 2H), 1.92 (m, 5H), 2.3 (s, 3H), 2.92 (d, 2H), 3.9 (s, 3H), 4.03 (d, 2H), 7.2 (s, 1H), 7.24 (s, partially obscured by $CHCl_3$ peak), 7.41 (m, 2H), 7.82 (s, 1H), 8.55 (s, 1H), 8.74 (s, 1H), 12.55 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

(c) DMF was used in place of methylene chloride as the reaction solvent. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.48 (m, 2H), 1.95 (m, 5H), 2.28 (s, 3H), 2.95 (d, 2H), 3.91 (s, 3H), 4.03 (d, 2H), 7.11 (s, 1H), 7.26 (s, 2H), 7.58 (s, 2H), 8.63 (s, 1H), 8.75 (s, 1H), 12.7 (s, 1H); Mass Spectrum: $M+H^+$ 490 and 492.

(d) Methylene chloride was used as the reaction solvent and the reaction mixture was heated to 35°C for 16 hours. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.2-1.4 (m, 2H), 1.7-1.8 (m, 4H), 1.85 (t, 1H), 2.1 (s, 3H), 2.8 (d, 2H), 3.9 (br s, 3H), 4.0 (br d, 2H), 7.2 (s, 1H), 7.4-7.45 (m, 2H), 7.5-7.55 (m, 2H), 7.6-7.7 (m, 2H), 8.0 (br s, 1H), 8.7 (br s, 1H); Mass Spectrum: $M+H^+$ 500 and 502.

(e) Methylene chloride was used as the reaction solvent and the reaction mixture was heated to 35°C for 16 hours. The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.7-1.8 (m, 4H), 1.85 (t, 1H), 2.1 (s, 3H), 2.7 (d, 2H), 3.9 (s, 3H), 4.0 (br d, 2H), 7.2 (s, 1H), 7.8 (d, 2H), 7.9 (s, 1H), 8.1 (d, 2H), 8.6 (br s, 1H), 10.2-10.5 (br s, 1H), 12.3-12.7 (br s, 1H); Mass Spectrum: $M+H^+$ 467.

Example 14 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-(*trans*-2-phenylcyclopropyl)urea

trans-2-Phenylcyclopropyl isocyanate (0.2 ml) was added to a stirred mixture of 4-amino-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (0.1 g) and chloroform (3 ml) and the resultant mixture was stirred at ambient temperature for 20 hours. The reaction mixture was diluted with chloroform (3 ml) and tris-(2-aminoethyl)amine polystyrene resin (0.5 g) was added. The mixture was stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and 2M methanolic ammonia as eluent. There was thus obtained the title compound (0.11 g); NMR Spectrum: ($CDCl_3$) 1.24–1.38 (m, 2H), 1.41–1.57 (m, 2H), 1.87–2.05 (m, 5H), 2.21 (m, 1H), 2.3 (s, 3H), 2.91 (d, 2H), 3.05 (m, 1H), 3.97 (s, 3H), 4.04 (d, 2H), 7.1–7.26 (m, 6H partially obscured by $CHCl_3$ peak), 7.34 (m, 1H), 8.66 (s, 1H), 8.72 (s, 1H), 10.31 (s, 1H); Mass Spectrum: $M+H^+$ 462.

Example 15 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-[(S)-(-)-α-methylbenzyl]urea

Using an analogous procedure to that described in Example 14, (S)-(-)-α-methylbenzyl isocyanate was reacted with 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline to give the title compound; NMR Spectrum: ($CDCl_3$) 1.4–1.56 (m, 2H), 1.61 (d, 3H), 1.84–2.05 (m, 5H), 2.31 (s, 3H), 2.91 (d, 2H), 3.88

(s, 3H), 4.04 (d, 2H), 5.2 (m, 1H), 7.23 (d, 2H), 7.3–7.41 (m, 5H), 8.66 (s, 1H), 8.7 (s, 1H), 10.58 (s, 1H); Mass Spectrum: $M+H^+$ 450.

Example 16 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-[(R)-(+)-α-methylbenzyl]urea

Using an analogous procedure to that described in Example 14, (R)-(+)-α-methylbenzyl isocyanate was reacted with 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline to give the title compound; NMR Spectrum: ($CDCl_3$) 1.39–1.56 (m, 2H), 1.64 (d, 3H), 1.86–2.05 (m, 5H), 2.3 (s, 3H), 2.9 (d, 2H), 3.9 (s, 3H), 4.01 (d, 2H), 5.19 (m, 1H), 7.24 (d, 2H), 7.32–7.41 (m, 5H), 8.44 (s, 1H), 8.67 (s, 1H), 10.5 (s, 1H); Mass Spectrum: $M+H^+$ 450.

Example 17 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-[1-(1-naphthyl)ethyl]urea

Using an analogous procedure to that described in Example 14, 1-(1-naphthyl)ethyl isocyanate was reacted with 4-amino-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline to give the title compound; NMR Spectrum: ($CDCl_3$) 1.41–1.57 (m, 2H), 1.76 (m, partially obscured by water peak), 1.86–2.05 (m, 5H), 2.02 (s, 3H), 2.91 (s, 2H), 3.87 (s, 3H), 4.02 (d, 2H), 5.95 (s, 1H), 7.19 (s, 1H), 7.23 (s, 1H), 7.39–7.52 (m, 3H), 7.6 (d, 1H), 7.71 (d, 1H), 7.84 (m, 1H), 8.12 (m, 1H), 8.57 (s, 1H), 8.64 (s, 1H), 10.67 (t, 1H); Mass Spectrum: $M+H^+$ 500.

Example 18 1-(3-cyano-6,7-dimethoxyquinolin-4-yl)-3-(2,6-dichlorophenyl)urea

A solution of 4-amino-3-cyano-6,7-dimethoxyquinoline (0.115 g) in DMF (2 ml) was added to a stirred mixture of sodium hydride (50% dispersion in mineral oil; 0.04 g) and DMF (3 ml) and the mixture was stirred at ambient temperature for 20 minutes. 2,6-Dichlorophenyl isocyanate (0.17 g) was added and the mixture was stirred at ambient temperature for 20 hours. A second portion of sodium hydride dispersion (0.08 g) was added followed, after 20 minutes, by more 2,6-dichlorophenyl isocyanate (0.3 g). The reaction mixture was stirred for a further 2 hours. Methanol (1 ml) was added and the mixture was partitioned between ethyl acetate (50 ml) and water (10 ml). The organic layer was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of ethyl

acetate and methanol as eluent. There was thus obtained the title compound (0.03 g); NMR Spectrum: ($DMSOd_6$) 4.05 (s, 6H), 7.4-7.8 (m, 4H), 8.08 (s, 2H), 9.22 (s, 1H); Mass Spectrum: $M+H^+$ 417 & 419.

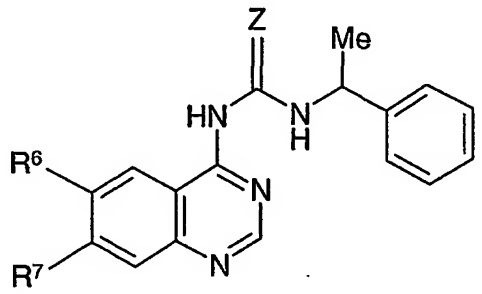
The 4-amino-3-cyano-6,7-dimethoxyquinoline used as a starting material was prepared as follows :-

A mixture of 4-chloro-3-cyano-6,7-dimethoxyquinoline (International Patent Application WO 98/43960; 1.24 g) and a 1M solution of ammonia gas in isopropanol (20 ml) was sealed in a Carius tube and heated to 120°C for 16 hours. The mixture was cooled to ambient temperature. A saturated aqueous sodium bicarbonate solution (50 ml) was added and the mixture was stirred for 15 minutes. The precipitate was isolated, washed with water (50 ml) and dried. There was thus obtained the required starting material (0.93 g); NMR Spectrum: ($DMSOd_6$) 3.88 (s, 3H), 3.9 (s, 3H), 7.2 (s, 1H), 7.63 (s, 2H), 7.69 (s, 1H), 8.38 (s, 1H); Mass Spectrum: $M+H^+$ 230.

Example 19

Using an analogous procedure to that described in Example 14, the appropriate 4-aminoquinazoline was, unless otherwise stated, reacted with (R)-(+)-α-methylbenzyl isocyanate to give the compounds described in Table IV.

Table IV



No.	R^6	R^7	Z	Note
1	methoxy	2-pyrrolidin-1-ylethoxy	O	(a)
2	methoxy	2-piperidinoethoxy	O	(b)
3	methoxy	2-piperidinoethoxy	O	(c)
4	methoxy	2-morpholinoethoxy	O	(d)
5	methoxy	2-(2-oxoimidazolidin-1-yl)ethoxy	O	(e)
6	methoxy	3-pyrrolidin-1-ylpropoxy	O	(f)

7	methoxy	3-piperidinopropoxy	O	(g)
8	methoxy	3-morpholinopropoxy	O	(h)
9	methoxy	3-(4-methylpiperazin-1-yl)propoxy	O	(i)
10	methoxy	2-(2-methoxyethoxy)ethoxy	O	(j)
11	3-piperidinopropoxy	methoxy	O	(k)
12	methoxy	N-methylpiperidin-4-ylmethoxy	S	(l)

Notes

(a) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.63 (d, 3H), 1.87 (s, 4H), 2.74 (s, 4H), 3.07 (t, 2H), 3.98 (s, 3H), 4.34 (t, 2H), 5.18 (m, 1H), 7.19–7.4 (m, 7H), 8.68 (d, 2H), 10.54 (d, 1H); Mass Spectrum: $M+H^+$ 436.

(b) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.66 (d, 7H), 2.54 (t, 4H), 2.9 (t, 2H), 3.89 (s, 3H), 4.3 (t, 2H), 5.19 (m, 1H), 7.2–7.4 (m, 7H), 8.68 (s, 1H), 8.8 (s, 1H), 10.55 (d, 1H); Mass Spectrum: $M+H^+$ 450.

(c) (S)-(-)-α-Methylbenzyl isocyanate was used in place of (R)-(+)-α-methylbenzyl isocyanate. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.62 (m, 7H), 2.56 (s, 4H), 2.9 (t, 2H), 3.88 (s, 3H), 4.31 (t, 2H), 5.17 (m, 1H), 7.19–7.41 (m, 7H), 8.68 (s, 1H), 8.8 (s, 1H), 10.55 (d, 1H); Mass Spectrum: $M+H^+$ 450.

(d) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4 (d, 3H), 2.65 (t, 4H), 3.05 (t, 2H), 3.75 (t, 4H), 3.87 (s, 3H), 4.31 (t, 2H), 5.18 (m, 1H), 7.14 (d, 2H), 7.19–7.41 (m, 5H), 8.68 (s, 1H), 8.85 (s, 1H), 10.54 (d, 1H); Mass Spectrum: $M+H^+$ 452.

(e) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.63 (d, 3H), 3.46 (t, 2H), 3.75 (m, 4H), 3.93 (s, 3H), 4.29 (t, 2H), 4.61 (s, 1H), 5.17 (m, 1H), 7.2–7.41 (m, 7H), 8.57 (s, 1H), 8.67 (s, 1H), 10.5 (d, 1H); Mass Spectrum: $M+H^+$ 451.

(f) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.62 (d, 3H), 1.87 (s, 4H), 2.2 (m, 2H), 2.7 (s, 4H), 2.8 (t, 2H), 3.91 (s, 3H), 4.24 (t, 2H), 5.18 (m, 1H), 7.2–7.27 (m, 2H), 7.29–7.32 (m, 5H), 8.44 (s, 1H), 8.67 (s, 1H), 10.47 (d, 1H); Mass Spectrum: $M+H^+$ 450.

(g) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.39 (m, 2H), 1.62 (d, 3H), 1.9 (s, 4H), 2.39 (t, 2H), 2.8–3.01 (br m, 6H), 3.9 (s, 3H), 4.24 (t, 2H), 5.14 (m, 1H), 7.1–7.44 (m, 7H), 8.45 (s, 1H), 8.65 (s, 1H), 10.45 (d, 1H); Mass Spectrum: $M+H^+$ 464.

(h) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.62 (d, 3H), 2.13 (m, 2H), 2.59 (m, 6H), 3.85 (t, 4H), 3.91 (s, 3H), 4.26 (t, 2H), 5.18 (m, 1H), 7.2–7.4 (m, 7H), 8.5 (s, 1H), 8.77 (s, 1H), 10.5 (d, 1H); Mass Spectrum: $M+H^+$ 466.

(i) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.62 (d, 3H), 1.76 (s, 4H), 2.1 (m, 2H), 2.31 (s, 3H), 2.4–2.6 (m, 6H), 3.92 (s, 3H), 4.24 (t, 2H), 5.19 (m, 1H), 7.21–7.41 (m, 7H), 8.49 (s, 1H), 8.68 (s, 1H), 10.5 (d, 1H); Mass Spectrum: $M+H^+$ 479.

(j) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.59 (d, 3H), 3.39 (s, 3H), 3.6 (m, 2H), 3.76 (m, 2H), 3.87 (s, 3H), 4.0 (t, 2H), 4.36 (t, 2H), 5.21 (m, 1H), 7.19–7.39 (m, 7H), 8.69 (s, 1H), 8.97 (s, 1H), 10.58 (d, 1H); Mass Spectrum: $M+H^+$ 441.

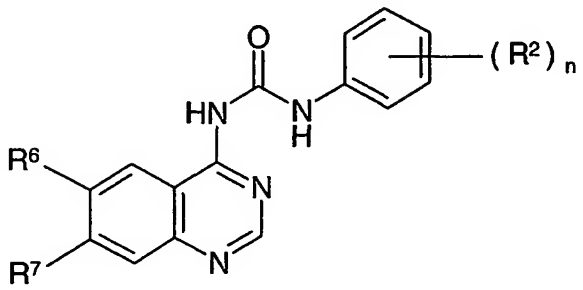
(k) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.38 (br s, 2H), 1.53 (m, 6H), 2.0 (m, 2H), 3.3-3.53 (br s, 6H), 3.95 (s, 3H), 4.17 (t, 2H), 5.04 (m, 1H), 7.25 (s, 1H), 7.37 (br m, 5H), 8.02 (s, 1H), 8.65 (s, 1H), 10.1 (s, 1H), 10.5 (d, 1H); Mass Spectrum: $M+H^+$ 464.

(l) The 4-aminoquinazoline was reacted with (R)-(+)-α-methylbenzyl isothiocyanate. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.42–1.57 (m, 2H), 1.71 (d, 3H), 1.86–2.06 (m, 5H), 2.31 (s, 3H), 2.92 (d, 2H), 4.02 (m, 5H), 5.69 (m, 1H), 6.98 (s, 1H), 7.24–7.31 (m, 2H), 7.34–7.47 (m, 4H), 8.54 (s, 1H), 8.65 (s, 1H), 12.57 (d, 1H); Mass Spectrum: $M+H^+$ 466.

Example 20

Using an analogous procedure to that described in Example 5, the appropriate 4-aminoquinazoline was reacted with the appropriate isocyanate to give the compounds described in Table V.

Table V



No.	R^6	R^7	$(R^2)_n$	Note
1	methoxy	3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy	2,6-dichloro	(a)
2	methoxy	3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy	2,6-difluoro	(b)

3	methoxy	3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy	2,6-dimethyl	(c)
4	methoxy	3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy	2-chloro-6-methyl	(d)

Notes

(a) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.2-1.35 (m, 2H), 1.43 (s, 9H), 1.6-1.72 (m, 3H), 1.94 (t, 2H), 2.0-2.15 (m, 2H), 2.52 (t, 2H), 2.9 (d, 2H), 3.02 (t, 2H), 3.6 (s, 3H), 4.23 (t, 2H), 4.6 (s, 1H), 7.1-7.3 (m, 3H), 7.38-7.43 (m, 2H), 8.7 (s, 1H), 9.38 (s, 1H), 12.38 (s, 1H); Mass Spectrum: $M+H^+$ 633 and 635.

The 4-amino-7-[3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 4-(4-bromo-2-fluorophenoxy)-7-(3-bromopropoxy)-6-methoxyquinazoline (0.486 g), 4-(tert-butoxycarbonylaminomethyl)piperidine (Chemical Abstracts Registry No. 135632-53-0, for example US Patent No. 5,864,039; 0.252 g), potassium carbonate (0.7 g) and DMF (10 ml) was stirred at 45°C for 20 hours. The solvent was evaporated and the residue was stirred with water (20 ml). The resultant solid was isolated and purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 2N solution of ammonia in methanol as eluent. There was thus obtained 4-(4-bromo-2-fluorophenoxy)-7-[3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazoline as a resinous solid (0.4 g); NMR Spectrum: ($CDCl_3$) 1.22-1.4 (m, 2H), 1.44 (s, 9H), 1.69 (m, 3H), 1.98 (t, 2H), 2.12 (m, 2H), 2.56 (t, 2H), 2.9-3.1 (m, 4H), 4.04 (s, 3H), 4.26 (t, 2H), 4.6 (br s, 1H), 7.22 (m, 1H), 7.3-7.45 (m, 3H), 7.51 (s, 1H), 8.67 (s, 1H); Mass Spectrum: $M+H^+$ 619 and 621.

A mixture of a portion (0.2 g) of the material so obtained and a saturated solution of ammonia in isopropanol (32 ml) was sealed in a Carius tube and heated at 110°C for 20 hours. The mixture was cooled to ambient temperature and the solvent was evaporated. The residue was stirred with a mixture of a 2N aqueous sodium hydroxide solution (5 ml), methylene chloride (18 ml) and methanol (2 ml) for 1 hour. The solid was isolated and dried. There was thus obtained the required starting material (0.046 g); NMR Spectrum: ($DMSOd_6$) 1.0-1.15 (m, 2H), 1.4 (m, 1H), 1.45 (s, 9H), 1.56 (d, 2H), 1.75-1.85 (m, 4H), 2.39 (d, 2H), 2.74-2.9 (m, 4H), 3.85 (s, 3H), 4.09 (t, 2H), 6.75 (br s, 1H), 7.02 (s, 1H), 7.32 (s, 2H), 7.54 (s, 1H), 8.24 (s, 1H); Mass Spectrum: $M+H^+$ 446.

(b) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.0-1.2 (m, 2H), 1.25-1.3 (m, 1H), 1.35 (s, 9H), 1.58 (d, 2H), 1.8-2.0 (m, 4H), 2.42 (t, 2H), 2.7-2.9 (m, 4H), 3.95 (s, 3H), 4.21 (t, 2H), 6.76 (t, 1H), 7.1-7.5 (m, 4H), 8.04 (s, 1H), 8.67 (s, 1H), 10.6 (s, 1H), 11.8 (s, 1H); Mass Spectrum: $M+H^+$ 601.

(c) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.2-1.4 (m, 3H), 1.43 (s, 9H), 1.9-2.15 (m, 4H), 2.33 (s, 6H), 2.52 (t, 2H), 2.92 (d, 4H), 3.02 (t, 2H), 3.38 (s, 3H), 4.21 (t, 2H), 4.6 (s, 1H), 7.05-7.15 (m, 4H), 7.48 (s, 1H), 8.66 (s, 1H), 9.64 (s, 1H), 11.9 (s, 1H); Mass Spectrum: $M+H^+$ 593.

(d) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.22-1.35 (m, 3H), 1.42 (s, 9H), 1.7 (m, 2H), 1.95 (t, 2H), 2.09 (m, 2H), 2.35 (s, 3H), 2.52 (t, 2H), 2.91 (d, 2H), 3.02 (t, 2H), 3.5 (s, 3H), 4.22 (t, 2H), 4.6 (s, 1H), 7.17 (m, 2H), 7.25-7.35 (m, 2H), 7.46 (s, 1H), 8.69 (s, 1H), 9.54 (s, 1H), 12.2 (s, 1H); Mass Spectrum: $M+H^+$ 613 and 615.

Example 21 1-{7-[3-(4-aminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2,6-dichlorophenyl)urea

A mixture of 1-{7-[3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2,6-dichlorophenyl)urea (0.075 g), trifluoroacetic acid (0.35 ml) and chloroform (1.5 ml) was stirred at ambient temperature for 40 minutes. The mixture was evaporated and the residue was stirred under a 1N aqueous sodium hydroxide solution (3 ml) for 1 hour. The resultant solid was isolated and dried. There was thus obtained the title compound (0.037 g); NMR Spectrum: ($DMSOd_6$) 1.12 (m, 3H), 1.62-1.7 (m, 2H), 1.9 (t, 2H), 2.0 (m, 4H), 2.38-2.54 (m, 4H), 2.92 (m, 2H), 3.3 (m, partially obscured by a water signal), 3.95 (s, 3H), 4.26 (t, 2H), 7.28 (s, 1H), 7.41 (t, 1H), 7.62 (d, 2H), 8.06 (s, 1H), 8.66 (s, 1H); Mass Spectrum: $M+H^+$ 533 and 535.

Example 22 1-{7-[3-(4-aminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2,6-difluorophenyl)urea

Using an analogous procedure to that described in Example 21, 1-{7-[3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2,6-difluorophenyl)urea was reacted with trifluoroacetic acid to give the title compound; NMR Spectrum: ($DMSOd_6$) 1.0-1.4 (m, 3H), 1.7 (d, 2H), 1.9-2.1 (m, 6H), 2.4 (m, 2H), 2.9 (d, 2H), 3.3 (s, partially obscured by a water signal), 4.0 (s, 3H), 4.24 (t, 3H), 5.0-7.0

(br m, 1H), 7.2-7.4 (m, 4H), 8.05 (s, 1H), 8.68 (s, 1H), 11.75 (s, 1H); Mass Spectrum: $M+H^+$ 501.

Example 23 1-{7-[3-(4-aminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2,6-dimethylphenyl)urea

Using an analogous procedure to that described in Example 21, 1-{7-[3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2,6-dimethylphenyl)urea was reacted with trifluoroacetic acid to give the title compound; NMR Spectrum: ($DMSOd_6$) 1.0-2.0 (m, 9H), 2.23 (s, 6H), 2.4 (m, 2H), 2.7-2.9 (m, 4H), 3.1-3.5 (partially obscured by a water signal), 3.93 (s, 3H), 4.18 (t, 2H), 6.9-7.15 (m, 4H), 7.23 (s, 1H), 8.03 (s, 1H), 8.62 (s, 1H), 11.7 (s, 1H); Mass Spectrum: $M+H^+$ 493.

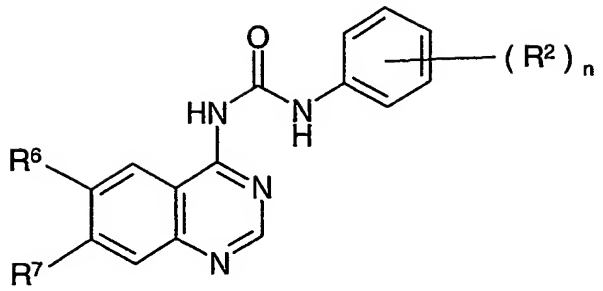
Example 24 1-{7-[3-(4-aminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2-chloro-6-methylphenyl)urea

Using an analogous procedure to that described in Example 21, 1-{7-[3-(4-tert-butoxycarbonylaminomethylpiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}-3-(2-chloro-6-methylphenyl)urea was reacted with trifluoroacetic acid to give the title compound; NMR Spectrum: ($DMSOd_6$) 1.0-1.3 (m, 3H), 1.63 (d, 2H), 1.7-2.0 (m, 4H), 2.28 (s, 3H), 2.4 (m, 2H), 2.86 (d, 2H), 3.1-3.5 (partially obscured by a water signal) 3.94 (s, 3H), 4.19 (t, 2H), 7.1-7.4 (m, 4H), 8.06 (s, 1H), 8.66 (s, 1H), 11.85 (s, 1H); Mass Spectrum: $M+H^+$ 513 and 515.

Example 25

Using an analogous procedure to that described in Example 1, the appropriate 4-aminoquinazoline was reacted with the appropriate isocyanate to give the compounds described in Table VI.

Table VI



No.	R^6	R^7	$(R^2)_n$	Note
1	3-morpholinopropoxy	methoxy	2-methyl	(a)
2	3-morpholinopropoxy	methoxy	2,6-dichloro	(b)
3	3-morpholinopropoxy	methoxy	2,6-difluoro	(c)
4	3-morpholinopropoxy	methoxy	2,6-dimethyl	(d)
5	3-piperidinopropoxy	methoxy	2,6-dichloro	(e)
6	3-piperidinopropoxy	methoxy	2,6-difluoro	(f)
7	3-piperidinopropoxy	methoxy	2,6-dimethyl	(g)
8	2-pyrrolidin-1-ylethoxy	methoxy	2,6-dichloro	(h)
9	N-(3-morpholinopropyl)carbamoyl	methoxy	2,6-dimethyl	(i)
10	2-(2-methoxyethoxy)ethoxy	methoxy	2,6-dichloro	(j)
11	2-(2-methoxyethoxy)ethoxy	methoxy	2,6-dimethyl	(k)

Notes

(a) The reaction product was dissolved in methylene chloride and treated with a saturated solution of hydrogen chloride gas in diethyl ether. The hydrochloride salt so obtained gave the following data: NMR Spectrum: ($DMSOd_6$ + CF_3CO_2D) 2.35 (m, 2H), 2.45 (s, 3H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 7.1 (m, 1H), 7.3 (m, 2H), 7.5 (s, 1H), 7.95 (d, 1H), 8.45 (s, 1H), 9.15 (s, 1H); Mass Spectrum: $M+H^+$ 452.

The 4-amino-7-methoxy-6-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (International Patent Application WO 96/33980, Example 1 therein; 6 g) and 6N aqueous hydrochloric acid solution (120 ml) was stirred and

heated to reflux for 6 hours. The mixture was cooled to 0°C and carefully, with cooling, was neutralised by the addition of concentrated aqueous ammonium hydroxide solution. The resultant precipitate was isolated, washed in turn with a dilute aqueous ammonium hydroxide solution and with water and dried under vacuum. There was thus obtained 7-methoxy-6-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (4.2 g); NMR Spectrum: ($DMSOd_6$) 2.4 (m, 6H), 3.59 (t, 4H), 3.75 (t, 2H), 3.9 (s, 3H), 4.12 (t, 2H), 7.12 (s, 1H), 7.43 (s, 1H), 7.98 (s, 1H), 12.0 (br s, 1H); Mass Spectrum: $M+H^+$ 320.

A mixture of a portion (0.99 g) of the material so obtained, thionyl chloride (10 ml) and DMF (0.1 ml) was stirred and heated to 80°C for 1.5 hours. The mixture was cooled to ambient temperature, toluene (10 ml) was added and the mixture was evaporated. The residue was partitioned between ethyl acetate and water (the acidity of the aqueous layer being adjusted to pH 7.5 by the addition of 2N aqueous sodium hydroxide solution). The organic layer was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. The solid so obtained was triturated under hexane, re-isolated and washed with diethyl ether. There was thus obtained 4-chloro-7-methoxy-6-(3-morpholinopropoxy)quinazoline (0.614 g); NMR Spectrum: ($CDCl_3$) 2.12 (m, 2H), 2.5 (br s, 4H), 2.59 (t, 2H), 3.73 (t, 4H), 4.05 (s, 3H), 4.27 (t, 2H), 7.33 (s, 1H), 7.4 (s, 1H), 8.86 (s, 1H).

A mixture of 4-chloro-7-methoxy-6-(3-morpholinopropoxy)quinazoline (1.6 g) and isopropanol (50 ml) was placed in a Carius tube which was cooled to -78°C prior to the addition of liquid ammonia (10 ml). The Carius tube was sealed and heated to 130°C for 20 hours. The Carius tube was cooled to ambient temperature, opened and the mixture was evaporated. The residue was triturated under diethyl ether. There was thus obtained 4-amino-7-methoxy-6-(3-morpholinopropoxy)quinazoline (containing 2.9 equivalents of ammonium chloride; 1.54 g) which was used without further purification. A portion of the material was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. The purified product gave the following data :- NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.5 (m, 6H), 3.6 (m, 4H), 3.9 (s, 3H), 4.1 (m, 2H), 7.05 (s, 1H), 7.4 (br s, 2H), 7.6 (s, 1H), 8.25 (s, 1H); Mass Spectrum: $M+H^+$ 319.

(b) The product gave the following data: NMR Spectrum: 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (d, 2H), 3.7 (t, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.45 (m, 2H), 7.65 (m, 2H), 8.3 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 506 and 508.

(c) The product gave the following data: NMR Spectrum: ($DMSOd_6$ + CF_3CO_2D) 2.3 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (d, 2H), 3.7 (t, 2H), 4.0 (m, 2H), 4.05 (m, 5H), 4.3 (m, 2H), 7.25 (m, 2H), 7.4 (m, 2H), 8.25 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 474.

(d) The product gave the following data: NMR Spectrum: ($DMSOd_6$ + CF_3CO_2D) 2.35 (m, 8H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (d, 2H), 3.7 (t, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 7.2 (m, 2H), 7.5 (s, 1H), 8.3 (s, 1H), 9.05 (s, 1H); Mass Spectrum: $M+H^+$ 466.

(e) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.4 (br s, 2H), 1.55 (br s, 4H), 2.04 (br s, 2H), 3.26-3.48 (m, 6H), 3.95 (s, 3H), 4.20 (t, 2H), 7.32 (s, 1H), 7.39 (t, 1H), 7.56 (m, 2H), 8.08 (s, 1H), 8.69 (s, 1H), 10.64 (s, 1H), 12.08 (s, 1H); Mass Spectrum: $M+H^+$ 504 and 506.

The 4-amino-7-methoxy-6-(3-piperidinopropoxy)quinazoline used as a starting material was prepared as follows :-

A mixture of 6-acetoxy-7-methoxyquinazolin-4-one (International Patent Application WO 96/15118, Example 39 thereof; 15 g), thionyl chloride (215 ml) and DMF (4.3 ml) was stirred and heated to 90°C for 4 hours. The mixture was cooled to ambient temperature and the thionyl chloride was evaporated. The material so obtained was dissolved in toluene and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic solution was dried over magnesium sulphate and evaporated. There was thus obtained 6-acetoxy-4-chloro-7-methoxyquinazoline (14.8 g) which was used without further purification.

A mixture of a portion (5 g) of the material so obtained, diphenylmethyleneamine (3.75 g), caesium carbonate (25.67 g) and xylene (200 ml) was stirred at ambient temperature for 30 minutes. Racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.227 g) and palladium diacetate (0.221 g) were added and the mixture was stirred and heated to 135°C for 16 hours. The mixture was cooled to ambient temperature and diethyl ether (600 ml) was added. The mixture was filtered and the filtrate was evaporated. There was thus obtained N-diphenylmethylene-6-acetoxy-7-methoxyquinazolin-4-amine (7.12 g); Mass Spectrum: $M+H^+$ 398.

A mixture of a portion (3.09 g) of the material so obtained, concentrated ammonium hydroxide solution (0.88 g/ml, approximately 14M; 60 ml) and methanol (120 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated. Toluene (200 ml) was added and the mixture was evaporated again. The residue was triturated under diethyl ether

(50 ml). There was thus obtained N-diphenylmethylene-6-hydroxy-7-methoxyquinazolin-4-amine (0.938 g); Mass Spectrum: $M+H^+$ 356.

A mixture of the material so obtained, 3-piperidinopropyl chloride (0.55 g), potassium carbonate (1.46 g) and DMF (50 ml) was stirred and heated to 65°C for 16 hours. The resultant mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic solution was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained N-diphenylmethylene-6-(3-piperidinopropoxy)-7-methoxyquinazolin-4-amine (0.277 g); NMR Spectrum: ($DMSOd_6$) 1.3 (br s, 2H), 1.42 (br s, 4H), 1.88 (t, 2H), 2.28 (br s, 4H), 2.38 (t, 2H), 3.92 (s, 3H), 4.07 (t, 2H), 7.0 (s, 1H), 7.23 (s, 1H), 7.2-7.65 (br m, 10H), 8.62 (s, 1H); Mass Spectrum: $M+H^+$ 481.

A mixture of the material so obtained, 3N aqueous hydrochloric acid solution (2 ml) and THF (14 ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was treated with a 2N aqueous sodium hydroxide solution (10 ml). The resultant precipitate was isolated, washed with water (10 ml) and dried under vacuum. There was thus obtained 4-amino-7-methoxy-6-(3-piperidinopropoxy)quinazoline (0.202 g); NMR Spectrum: ($DMSOd_6$) 1.36 (br s, 2H), 1.47(br s, 4H), 1.93 (t, 2H), 2.25-2.43 (br m, 6H), 3.88 (s, 3H), 4.05 (t, 2H), 7.04 (s, 1H), 7.35 (br s, 2H), 7.55 (s, 1H), 8.23 (s, 1H); Mass Spectrum: $M+H^+$ 317.

(f) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.4 (br s, 2H), 1.53 (br s, 4H), 2.02 (br s, 2H), 3.24-3.47 (br s, 6H), 3.97 (s, 3H), 4.23 (t, 2H), 7.22 (m, 2H), 7.31 (s, 1H), 7.4 (m, 1H), 8.05 (s, 1H), 8.69 (s, 1H), 10.67 (s, 1H), 11.82 (s, 1H); Mass Spectrum: $M+H^+$ 472.

(g) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.38 (br s, 2H), 1.5 (br s, 4H), 1.96 (m, 2H), 2.25 (s, 6H), 2.3-2.48 (br m, 6H), 3.96 (s, 3H), 4.15 (t, 2H), 7.14 (m, 3H), 7.3 (s, 1H), 8.07 (s, 1H), 8.67 (s, 1H), 10.38 (s, 1H), 11.69 (s, 1H); Mass Spectrum: $M+H^+$ 464.

(h) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.72 (br s, 4H), 2.67 (br s, 4H), 2.97 (br s, 2H), 3.99 (s, 3H), 4.3 (t, 2H), 7.31 (s, 1H), 7.37 (t, 1H), 7.59 (d, 2H), 8.07 (s, 1H), 8.72 (s, 1H), 10.52 (s, 1H), 12.06 (s, 1H); Mass Spectrum: $M+H^+$ 476 and 478.

The 4-amino-7-methoxy-6-(2-pyrrolidin-1-ylethoxy)quinazoline used as a starting material was prepared from N-diphenylmethylene-6-hydroxy-7-methoxyquinazolin-4-amine

and 2-pyrrolidin-1-ylethyl chloride using analogous procedures to those described in the last two paragraphs of Note (e) above. The material so obtained gave the following data :- NMR Spectrum: ($DMSOd_6$) 1.68 (m, 4H), 2.58 (m, 6H), 3.86 (s, 3H), 4.15 (t, 2H), 7.05 (s, 1H), 7.33 (s, 1H), 8.24 (s, 1H); Mass Spectrum: $M+H^+$ 289.

(i) Chloroform was used as the reaction solvent. Triethylamine (1 equivalent) was also added. The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.99 (t, 2H), 2.37 (s, 6H), 2.7 (m, 4H), 3.63 (q, 2H), 3.79 (m, 6H), 4.15 (s, 3H), 7.13 (s, 3H), 7.4 (s, 1H), 8.0 (t, 1H), 8.2 (s, 1H), 8.79 (s, 1H), 8.9 (s, 1H), 11.2 (s, 1H); Mass Spectrum: $M+H^+$ 493.

The 4-amino-7-methoxy-6-[N-(3-morpholinopropyl)carbamoyl]quinazoline used as a starting material was prepared as follows :-

Methyl 4-amino-5-cyano-2-hydroxybenzoate (J. Chem. Soc. Perkin I, 1979, 677; 4 g) was added to stirred concentrated sulphuric acid (6 ml) and the mixture was heated to 80°C for 30 minutes. The mixture was cooled to ambient temperature and poured onto crushed ice. The resultant solid was filtered off, washed well with water and dried to give methyl 4-amino-5-carbamoyl-2-hydroxybenzoate (2.8 g); NMR Spectrum: ($DMSOd_6$) 3.83 (s, 3H), 6.1 (s, 1H), 6.75 (br m, 2H), 8.08 (s, 1H).

A mixture of methyl 4-amino-5-carbamoyl-2-hydroxybenzoate (5.4 g) and formic acid (50 ml) was heated to reflux for 1hour. The mixture was evaporated. Toluene (75ml) was added and the mixture was evaporated. The solid residue was washed with methanol and diethyl ether and dried to give methyl 7-hydroxy-4-oxo-3,4-dihydroquinazoline-6-carboxylate (5.2 g); NMR Spectrum: ($DMSOd_6$) 4.9 (s, 3H), 7.09 (s, 1H), 7.39 (s, 1H), 8.5 (s, 1H).

A mixture of methyl 7-hydroxy-4-oxo-3,4-dihydroquinazoline-6-carboxylate (17.7 g) and acetic anhydride (200 ml) was heated to 120°C for 1.5 hours. The mixture was evaporated. Toluene (75ml) was added and the mixture was re-evaporated. There was thus obtained methyl 7-acetoxy-4-oxo-3,4-dihydroquinazoline-6-carboxylate (20.7 g); NMR Spectrum: ($DMSOd_6$) 2.33 (s, 3H), 3.86 (s, 3H), 7.5 (s, 1H), 8.28 (s, 1H), 8.68 (s, 1H); Mass Spectrum: $M+H^+$ 263.

A mixture of a portion (7.2 g) of the material so obtained and thionyl chloride (75 ml) was heated to reflux for 1hourr. The excess thionyl chloride was evaporated. Toluene (50 ml) was added and the mixture was re-evaporated. The residue was dissolved in methylene chloride and treated with triethylamine (3.34 g). The mixture was passed through a silica gel column (40 g) using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained methyl 7-acetoxy-4-chloroquinazoline-6-carboxylate

(6.88 g); NMR Spectrum: ($CDCl_3$) 2.43 (s, 3H), 4.0 (s, 3H), 7.8 (s, 1H), 8.99 (s, 1H), 9.12 (s, 1H).

A mixture of a portion (2.74 g) of the material so obtained, 2,4,6-trimethoxybenzylamine (3.86 g) and methylene chloride (90 ml) was allowed to stand at ambient temperature for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated under diethyl ether. The resultant solid was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained methyl 7-hydroxy-4-(2,4,6-trimethoxybenzylamino)quinazoline-6-carboxylate (3.25 g); NMR Spectrum: ($DMSOd_6$) 3.85 (s, 9H), 3.98 (s, 3H), 4.82 (d, 2H), 6.2 (s, 1H), 7.25 (s, 1H), 7.27 (s, 1H), 8.27 (s, 1H), 8.67 (s, 1H), 10.73 (s, 1H); Mass Spectrum: $M+H^+$ 400.

(Trimethylsilyl)diazomethane (2M in hexane, 10 ml) was added to a mixture of the material so obtained, di-isopropylethylamine (1.26 g), methanol (10 ml) and methylene chloride (30 ml) and the resultant mixture was stirred at ambient temperature for 3 hours. The reaction mixture was treated with a second aliquot of (trimethylsilyl)diazomethane solution (10 ml) and stirred for a further 18 hours. Silica gel (2 g) was added cautiously and the mixture was stirred for 5 minutes. The mixture was evaporated and the reaction product (adsorbed onto silica) was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained methyl 7-methoxy-4-(2,4,6-trimethoxybenzylamino)quinazoline-6-carboxylate (1.244 g); Mass Spectrum: $M+H^+$ 414.

A mixture of a portion (0.295 g) of the material so obtained and N-(3-aminopropyl)morpholine (0.5 ml) was stirred and heated to 150°C for 1 hour. The mixture was partitioned between methylene chloride and water. The organic solution was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(2,4,6-trimethoxybenzylamino)-7-methoxy-6-[N-(3-morpholinopropyl)carbamoyl]quinazoline (0.144 g) Mass Spectrum: $M+H^+$ 526.

Trifluoroacetic acid (1 ml) was added to a mixture of the material so obtained, triethylsilane (0.093 g) and methylene chloride (0.15 ml) and the reaction mixture was stirred and heated to reflux for 2 minutes. The mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic soultion was evaporated to

give 4-amino-7-methoxy-6-[N-(3-morpholinopropyl)carbamoyl]quinazoline (0.129 g); Mass Spectrum: $M+H^+$ 346.

(j) The product gave the following data: NMR Spectrum: ($CDCl_3$) 3.39 (s, 3H), 3.6 (m, 2H), 3.75 (m, 2H), 3.86 (m. 2H), 4.02 (s, 3H), 4.07 (m, 2H), 7.21 (t, 1H), 7.29 (s, 1H), 7.39 (d, 2H), 7.51 (s, 1H), 8.73 (s, 1H), 9.14 (s, 1H), 12.19 (s, 1H); Mass Spectrum: $M+H^+$ 481 and 483.

The 4-amino-7-methoxy-6-[2-(2-methoxyethoxy)ethoxy]quinazoline used as a starting material was prepared from N-diphenylmethylene-6-hydroxy-7-methoxyquinazolin-4-amine and 2-(2-methoxyethoxy)ethyl chloride using analogous procedures to those described in the last two paragraphs of Note (e) above. In a further preparation, 2-(2-methoxyethoxy)ethyl 4-toluenesulphonate was used. The required starting material gave the following data: NMR Spectrum: ($CDCl_3$) 3.4 (s, 3H), 3.61 (m, 2H), 3.72 (m, 2H), 3.93 (m, 2H), 3.99 (s, 3H), 4.34 (m, 2H), 5.67 (br s, 2H), 7.2 (s,1H), 7.32 (s, 1H), 8.5 (s, 1H); Mass Spectrum: $M+H^+$ 294.

(k) The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.31 (s, 6H), 3.38 (s, 3H), 3.6 (m, 2H), 3.69 (m, 4H), 3.85 (m, 2H), 4.14 (s, 3H), 7.12 (m, 4H), 7.58 (s, 1H), 8.68 (s, 1H), 9.44 (s, 1H), 11.77 (s, 1H); Mass Spectrum: $M+H^+$ 441.

Example 26 1-(2,6-dichlorophenyl)-3-[6-methoxy-7-(6-methylamino-1-hexynyl)quinazolin-4-yl]urea

A mixture of 1-(2,6-dichlorophenyl)-3-{7-[6-(N-tert-butoxycarbonylamino-N-methylamino)-1-hexynyl]-6-methoxyquinazolin-4-yl}urea (0.1 g), trifluoroacetic acid (1 ml) and methylene chloride (1 ml) was stirred at ambient temperature for 1.5 hours. The mixture was evaporated and a solution of hydrogen chloride gas in ethyl acetate was added. Toluene was added and the mixture was evaporated. The residue was triturated under diethyl ether and the resultant solid was isolated. There was thus obtained the title compound as the hydrochloride salt (0.095g); NMR Spectrum: ($DMSOd_6$) 1.65 (m, 2H), 1.78 (m, 2H), 2.55 (m, 5H), 2.95 (m, 2H), 4.0 (s, 3H), 7.38 (t, 1H), 7.6 (d, 2H), 7.89 (s, 1H), 8.16 (s, 1H), 8.7 (m, 3H), 10.9 (br, 1H), 11.8 (s, 1H); Mass Spectrum: $M+H^+$ 472 and 474.

The 1-(2,6-dichlorophenyl)-3-{7-[6-(N-tert-butoxycarbonylamino)-N-methylamino-1-hexynyl]-6-methoxyquinazolin-4-yl}urea used as a starting material was prepared as follows :-

Using an analogous procedure to that described in the second last paragraph of Note [115] in Example 2 above, 6-(N-tert-butoxycarbonylamino-N-methylamino)-1-hexyne

was reacted with 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-trifluoromethanesulphonyloxyquinazoline to give 4-(2-bromo-4-fluorophenoxy)-6-methoxy-7-[6-(N-tert-butoxycarbonylamino)-N-methylamino-1-hexynyl]quinazoline; NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 1.55 (m, 2H), 1.65 (m, 2H), 2.57 (t, 2H), 2.79 (s, 3H), 3.24 (t, 2H), 4.0 (s, 3H), 7.35-7.82 (m, 3H), 7.65 (s, 1H), 7.95 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 558 and 560.

The material so obtained was reacted with ammonia using an analogous procedure to that described in the last paragraph of Note [115] in Example 2 above, except that the ammonia reaction was carried out at 110°C rather than at 130°C. There was thus obtained 4-amino-6-methoxy-7-[6-(N-tert-butoxycarbonylamino)-N-methylamino-1-hexynyl]quinazoline.

The material so obtained was reacted with 2,6-dichlorophenyl isocyanate using an analogous procedure to that described in Example 1. There was thus obtained the required starting material; NMR Spectrum: ($DMSOd_6$) 1.39 (s, 9H), 1.55 (m, 2H), 1.67 (m, 2H), 2.56 (m, 2H), 2.79 (s, 3H), 3.2 (m, 2H), 3.97 (s, 3H), 7.4 (m, 1H), 7.6 (m, 2H), 7.84 (s, 1H), 8.14 (s, 1H), 8.75 (s, 1H), 10.8 (s, 1H), 11.95 (s, 1H).

The 6-(N-tert-butoxycarbonylamino-N-methylamino)-1-hexyne used as a starting material was prepared as follows :-

6-Mesyloxy-1-hexyne was reacted with methylamine using an analogous procedure to that described in J. Heterocyclic Chemistry, 1994, 31, 1421 to give 6-methylamino-1-hexyne which was reacted di-tert-butyl dicarbonate using a conventional procedure.

Example 27 1-(2,6-dimethylphenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]thiourea

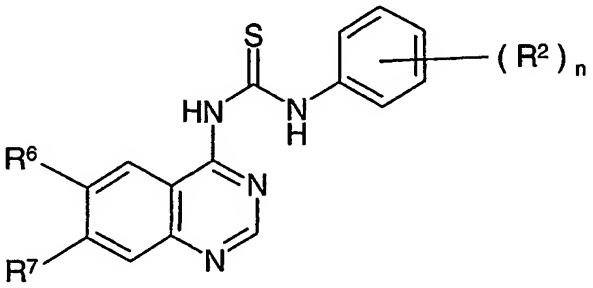
A solution of 4-amino-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (150 mg) in DMF (4.5 ml) was added to sodium hydride (60% dispersion in mineral oil, 0.03 g) and the reaction mixture was stirred at ambient temperature for 20 minutes. 2,6-Dimethylphenyl isothiocyanate (0.162 g) was added and the mixture was stirred at ambient temperature for 20 hours. The reaction mixture was evaporated and the residual solid was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 2M solution of ammonia in methanol as eluent. There was thus obtained the title compound (0.112 g); NMR Spectrum: ($CDCl_3$) 1.44–1.61 (m, 2H), 1.87–

2.08 (m, 5H), 2.32 (s, 3H), 2.36 (s, 6H), 2.94 (d, 2H), 4.04 (m, 5H), 7.1 (s, 1H), 7.19 (m, 3H), 7.29 (s, 1H), 8.69 (s, 1H), 8.9 (s, 1H), 13.37 (s, 1H); Mass Spectrum: $M+H^+$ 466.

Example 28

Using an analogous procedure to that described in Example 27, the appropriate 4-aminoquinazoline was reacted with the appropriate isothiocyanate to give the compounds described in Table VII.

Table VII



No.	R^6	R^7	$(R^2)_n$	Note
1	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-dichloro	(a)
2	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-difluoro	(b)
3	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro-6-methyl	(c)
4	methoxy	N-methylpiperidin-4-ylmethoxy	2,4,6-trichloro	(d)
5	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-dimethyl-4-bromo	(e)
6	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-dimethyl	(f)
7	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-dichloro	(g)
8	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-difluoro	(h)
9	methoxy	3-pyrrolidin-1-ylpropoxy	2-chloro-6-methyl	(i)
10	methoxy	2-(2-methoxyethoxy)ethoxy	2,6-dimethyl	(j)
11	methoxy	2-morpholinoethoxy	2,6-dimethyl	(k)
12	methoxy	3-morpholinopropoxy	2,6-dimethyl	(l)
13	methoxy	cyclopropylmethoxy	2,6-dimethyl	(m)
14	methoxy	2-morpholinoethoxy	2-chloro-6-methyl	(n)
15	methoxy	3-morpholinopropoxy	2-chloro-6-methyl	(o)
16	methoxy	N-methylpiperidin-4-ylmethoxy	2-methyl	(p)

17	methoxy	2-pyrrolidin-1-ylethoxy	2,6-dimethyl	(q)

Notes

(a) The product gave the following data: Mass Spectrum: $M+H^+$ 506 and 508.

(b) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.43–1.6 (m, 2H), 1.83–2.09 (m, 5H), 2.33 (s, 3H), 2.94 (d, 2H), 4.04 (m, 5H), 7.0–7.14 (m, 4H), 7.27 (m, 1H), 7.35 (m, 1H), 8.7 (s, 1H), 13.49 (s, 1H); Mass Spectrum: $M+H^+$ 474.

(c) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.45–1.61 (m, 2H), 1.87–2.11 (m, 5H), 2.31 (s, 3H), 2.42 (s, 2H), 3.97 (d, 2H), 4.02 (m, 5H), 7.07 (s, 1H), 7.2–7.3 (m, 3H), 7.38 (t, 1H), 8.7 (s, 1H), 8.9 (s, 1H) 13.51 (s, 1H); Mass Spectrum: $M+H^+$ 486 and 488.

(d) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.48–1.61 (m, 2H), 1.88–2.16 (m, 5H), 2.36 (s, 3H), 3.0 (d, 2H), 4.07 (m, 5H), 7.11 (s, 1H), 7.3 (d, 2H), 7.43 (s, 1H), 7.49 (s, 1H), 8.72 (s, 1H) 13.71 (s, 1H); Mass Spectrum: $M+H^+$ 540 and 543.

(e) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.47–1.61 (m, 2H), 1.87–2.11 (m, 5H), 2.32 (d, 9H), 2.99 (d, 2H), 4.04 (m, 5H), 7.1 (s, 1H), 7.3 (s, 1H), 7.32 (s, 1H), 8.7 (s, 1H), 8.9 (s, 1H), 13.31 (s, 1H); Mass Spectrum: $M+H^+$ 544 and 546.

(f) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.44–1.59 (m, 2H), 1.88–2.07 (m, 5H), 2.31 (s, 3H), 2.35 (d, 6H), 2.94 (d, 2H), 4.04 (m, 5H), 7.08 (d, 1H), 7.2 (d, 1H), 7.29 (s, 1H), 7.55 (s, 1H), 8.68 (s, 1H), 8.77 (s, 1H), 13.63 (s, 1H); Mass Spectrum: $M+H^+$ 466.

(g) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.83 (s, 4H), 2.21 (m, 2H), 2.63 (s, 4H), 2.76 (t, 2H), 4.03 (s, 3H), 4.29 (t, 2H), 7.08 (t, 1H), 7.27–7.33 (s, 2H), 7.44 (m, 3H), 8.73 (s, 1H), 13.7 (s, 1H); Mass Spectrum: $M+H^+$ 506 and 508.

(h) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.83 (s, 4H), 2.2 (m, 2H), 2.61 (s, 4H), 2.74 (t, 2H), 4.04 (s, 3H), 4.48 (t, 2H), 6.98–7.11 (m, 3H), 7.27–7.41 (m, 3H), 8.71 (s, 1H), 13.48 (s, 1H); Mass Spectrum: $M+H^+$ 474.

(i) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H), 2.18 (m, 2H), 2.4 (s, 3H), 2.55 (m, 4H), 2.68 (t, 2H), 4.02 (s, 3H), 4.3 (t, 2H), 7.07 (s, 1H), 7.26 (m, 2H), 7.31 (s, 1H), 7.37 (m, 1H), 8.7 (s, 1H), 8.94 (br s, 1H), 13.51 (s, 1H); Mass Spectrum: $M+H^+$ 486 and 488.

(j) The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.35 (s, 6H), 3.4 (s, 3H), 3.6 (m, 2H), 3.87 (m, 2H), 4.03 (t, 2H), 4.05 (s, 3H), 4.37 (t, 2H), 7.09 (s, 1H), 7.14–7.21 (m, 3H), 7.33 (s, 1H), 8.68 (s, 1H), 8.84 (s, 1H), 13.32 (s, 1H); Mass Spectrum: $M+H^+$ 457.

(k) The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.36 (s, 6H), 2.61 (t, 4H), 2.95 (t, 2H), 3.77 (t, 4H), 4.04 (s, 3H), 4.34 (t, 2H), 7.11 (s, 1H), 7.2 (m, 3H), 7.31 (s, 1H), 8.69 (s, 1H), 8.9 (s, 1H), 13.36 (s, 1H); Mass Spectrum: $M+H^+$ 468.

(l) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H), 2.4 (s, 4H), 2.45 (t, 2H), 3.58 (t, 4H), 4.03 (s, 3H), 4.21 (t, 2H), 7.18 (m, 3H), 7.33 (s, 1H), 8.19 (s, 1H), 8.71 (s, 1H), 11.09 (s, 1H), 13.7 (s, 1H); Mass Spectrum: $M+H^+$ 482.

(m) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 0.39 (m, 2H), 0.61 (m, 2H), 1.32 (m, 1H), 2.25 (s, 6H), 4.0 (m, 5H), 7.17 (s, 3H), 7.25 (s, 1H), 8.17 (s, 1H), 8.72 (s, 1H), 11.08 (br s, 1H), 13.67 (s, 1H); Mass Spectrum: $M+H^+$ 409.

(n) The product gave the following data: Mass Spectrum: $M+H^+$ 488 and 490.

(o) The product gave the following data: Mass Spectrum: $M+H^+$ 502 and 504.

(p) The product gave the following data: Mass Spectrum: $M+H^+$ 452.

(q) The product gave the following data: Mass Spectrum: $M+H^+$ 452.

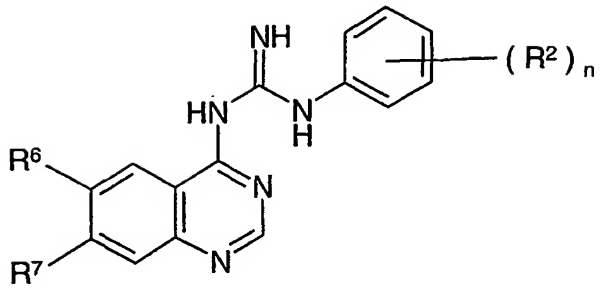
Example 29 1-(2,6-dimethylphenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]guanidine

Mercuric(II) oxide (0.059 g) was added to a mixture of 1-(2,6-dimethylphenyl)-3-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]thiourea (0.105 g), a 2M solution of ammonia in methanol (3 ml) and chloroform (1 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 2M solution of ammonia in methanol as eluent. There was thus obtained the title compound (0.074 g); NMR Spectrum: ($CDCl_3$) 1.39–1.53 (m, 2H), 1.87–2.02 (q, 5H), 2.29 (s, 3H), 2.36 (s, 6H), 2.9 (d, 2H), 4.01 (m, 5H), 5.79 (br s, 1H), 7.16 (s, 1H), 7.19 (m, 3H), 7.87 (s, 1H), 8.57 (s, 1H); Mass Spectrum: $M+H^+$ 449.

Example 30

Using an analogous procedure to that described in Example 29, the appropriate quinazoline-4-thiourea was reacted with ammonia to give the guanidines described in Table VIII.

Table VIII



No.	R^6	R^7	$(R^2)_n$	Note
1	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-dichloro	(a)
2	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-difluoro	(b)
3	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro-6-methyl	(c)
4	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-dimethyl-4-bromo	(d)
5	methoxy	N-methylpiperidin-4-ylmethoxy	2,5-dimethyl	(e)
6	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-dichloro	(f)
7	methoxy	3-pyrrolidin-1-ylpropoxy	2,6-difluoro	(g)
8	methoxy	3-pyrrolidin-1-ylpropoxy	2-chloro-6-methyl	(h)
9	methoxy	2-(2-methoxyethoxy)ethoxy	2,6-dimethyl	(i)
10	methoxy	2-morpholinoethoxy	2,6-dimethyl	(j)
11	methoxy	cyclopropylmethoxy	2,6-dimethyl	(k)
12	methoxy	2-pyrrolidin-1-ylethoxy	2,6-dimethyl	(l)
13	methoxy	N-methylpiperidin-4-ylmethoxy	2-methyl	(m)

Notes

(a) The product gave the following data: NMR Spectrum: ($DMSOd_6$, 100°C) 1.4 (m, 2H), 1.78 (m, 3H), 1.96 (t, 2H), 2.2 (s, 3H), 2.8 (m, 2H), 3.76 (s, 3H), 4.0 (d, 2H), 7.11 (s, 1H), 7.28 (t, 2H), 7.47 (s, 1H), 7.54 (d, 2H), 7.98 (s, 1H), 8.5 (s, 1H), 9.0 (br s, 1H); Mass Spectrum: $M+H^+$ 489 and 491.

(b) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 1.34 (m, 2H), 1.73 (d, 3H), 1.88 (t, 2H), 2.16 (s, 3H), 2.79 (d, 2H), 3.3 (s, 2H), 3.69 (s, 3H), 3.95 (d, 2H), 7.07 (s, 1H), 7.2 (t, 2H), 7.34 (br s, 1H), 8.49 (s, 1H), 8.74 (s, 1H); Mass Spectrum: $M+H^+$ 457.

(c) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.4–1.56 (m, 2H), 1.87–2.05 (q, 5H), 2.3 (s, 3H), 2.4 (s, 3H), 2.9 (d, 2H), 3.98–4.05 (m, 5H), 7.13–7.27 (m, 3H), 7.38 (m, 1H), 7.81 (s, 1H), 8.59 (s, 1H); Mass Spectrum: $M+H^+$ 469 and 471.

(d) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.38–1.54 (m, 2H), 1.82–2.02 (q, 5H), 2.28 (s, 3H), 2.32 (s, 6H), 2.89 (d, 2H), 4.0 (m, 5H), 5.7 (br s, 1H), 7.03–7.27 (m, 3H), 7.32 (s, 2H), 7.81 (s, 1H), 8.57 (s, 1H); Mass Spectrum: $M+H^+$ 526 and 528.

(e) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.39–1.44 (m, 2H), 1.87–2.04 (q, 5H), 2.29 (s, 3H), 2.34 (d, 6H), 2.89 (d, 2H), 4.02 (m, 5H), 6.19 (br s, 1H), 7.05 (d, 1H), 7.14 (s, 2H), 7.2 (d, 1H), 7.84 (s, 1H), 8.57 (s, 1H); Mass Spectrum: $M+H^+$ 449.

(f) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H), 2.17 (m, 2H), 2.53 (s, 4H), 2.67 (t, 2H), 3.99 (s, 3H), 4.25 (t, 2H), 7.1 (t, 1H), 7.2 (s, 1H), 7.41 (d, 1H), 7.51 (s, 1H), 8.57 (s, 1H); Mass Spectrum: $M+H^+$ 489 and 491.

(g) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.79 (m, 4H), 2.14 (m, 2H), 2.53 (m, 4H), 2.67 (t, 2H), 3.97 (s, 3H), 4.24 (t, 2H), 7.03 (t, 2H), 7.2 (m, 2H), 7.63 (s, 1H), 8.59 (s, 1H); Mass Spectrum: $M+H^+$ 457.

(h) The product gave the following data: NMR Spectrum: ($CDCl_3$) 1.79 (m, 4H), 2.15 (m, 2H), 2.4 (s, 3H), 2.56 (s, 4H), 2.68 (t, 2H), 3.98 (s, 3H), 4.26 (t, 2H), 6.13 (br s, 1H), 7.14–7.26 (m, 3H), 7.37 (m, 1H), 7.82 (s, 1H), 8.58 (s, 1H); Mass Spectrum: $M+H^+$ 469 and 471.

(i) The product gave the following data: NMR Spectrum: ($CDCl_3$) 2.35 (s, 6H), 3.4 (s, 3H), 3.61 (m, 2H), 3.77 (m, 2H), 3.99 (m, 5H), 4.34 (t, 2H), 5.76 (br s, 1H), 7.17 (m, 4H), 7.87 (s, 1H), 8.56 (s, 1H); Mass Spectrum: $M+H^+$ 440.

(j) The product gave the following data: NMR Spectrum: ($DMSOd_6$, 100°C) 2.29 (s, 6H), 2.53 (m, 4H), 2.79 (t, 2H), 3.6 (t, 4H), 3.74 (s, 3H), 4.22 (t, 2H), 7.09 (s, 1H), 7.16 (s, 3H), 7.51 (s, 1H), 7.7 (s, 2H), 8.45 (s, 1H), 8.88 (br s, 1H); Mass Spectrum: $M+H^+$ 451.

(k) The product gave the following data: NMR Spectrum: ($CDCl_3$) 0.34 (m, 2H), 0.63 (m, 2H), 1.37 (m, 1H), 2.28 (s, 6H), 3.93 (d, 2H), 3.97 (s, 3H), 5.9 (br m, 1H), 7.07 (s, 1H), 7.12 (m, 4H), 7.79 (s, 1H), 8.48 (s, 1H); Mass Spectrum: $M+H^+$ 392.

(l) The product gave the following data: Mass Spectrum: $M+H^+$ 435.

(m) The product gave the following data: Mass Spectrum: $M+H^+$ 435.

Example 31 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-[(R)-(+)-α-methylbenzyl]guanidine

Using an analogous procedure to that described in Example 29, 1-[6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]-3-[(R)-(+)-α-methylbenzyl]thiourea was reacted with ammonia to give the title compound; NMR Spectrum: ($CDCl_3$) 1.38–1.42 (m,

2H), 1.61 (d, 3H), 1.86–2.01 (q, 5H), 2.29 (s, 3H), 2.89 (d, 2H), 3.95 (m, 3H), 4.0 (d, 2H), 4.7 (q, 1H), 6.5 (br s, 1H), 7.12 (s,1H), 7.29-7.31 (m, 5H), 7.79 (s, 1H), 8.53 (s, 1H); Mass Spectrum: $M+H^+$ 449.

Example 32 **1-(2-aminophenyl)-3-(6,7-dimethoxyquinazolin-4-yl)urea**

A mixture of 1-(6,7-dimethoxyquinazolin-4-yl)-3-(2-nitrophenyl)urea (0.18 g), 10% palladium-on-charcoal catalyst (0.023 g) and DMF (10 ml) was stirred at ambient temperature under an atmosphere of hydrogen for 16 hours. The reaction mixture was filtered and the filtrate was evaporated. The resultant gum was triturated under ethyl acetate and there was thus obtained the title compound as a solid (0.137 g); NMR Spectrum: ($DMSOd_6$) 3.85-3.95 (br s, 8H), 6.63 (t, 1H), 6.81 (d, 1H), 6.91 (t, 1H), 7.25 (s, 1H), 7.47 (d, 1H), 8.05 (s, 1H), 8.64 (s, 1H), 10.28 (br s, 1H), 11.74 (br s, 1H); Mass Spectrum: $M+H^+$ 340.

The 1-(6,7-dimethoxyquinazolin-4-yl)-3-(2-nitrophenyl)urea used as a starting material was prepared by the reaction of 2-nitrophenylisocyanate and 4-amino-6,7-dimethoxyquinazoline using an analogous procedure to that described in Example 1. There was thus obtained the required starting material in 62% yield; NMR Spectrum: ($DMSOd_6$) 3.95 (s, 6H), 7.3 (s, 1H), 7.28-7.35 (t, 1H), 7.74 (t, 1H), 8.05 (s, 1H), 8.13 (m, 1H), 8.51 (m, 1H), 8.72 (s, 1H), 10.61 (s, 1H), 13.67 (br s, 1H); Mass Spectrum: $M+H^+$ 370.

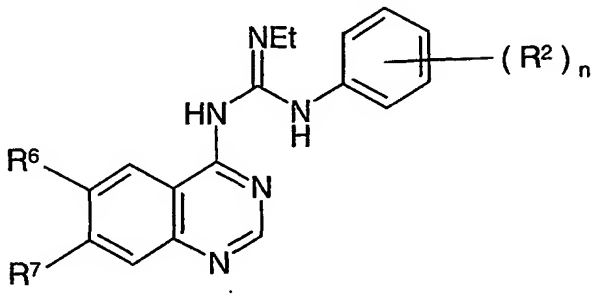
Example 33 **1-(2,6-dichlorophenyl)-3-(6-methoxy-7-piperazin-1-ylquinazolin-4-yl)urea**

A mixture of 1-(2,6-dichlorophenyl)-3-{6-methoxy-7-[N-(tert-butoxycarbonyl)piperazin-1-yl]quinazolin-4-yl}urea (0.075 g), trifluoroacetic acid (1 ml) and methylene chloride (1 ml) was stirred at ambient temperature for 1 hour. The resultant mixture was evaporated. A saturated solution of hydrogen chloride gas in ethyl acetate was added and the mixture was evaporated. The resultant solid was triturated under diethyl ether, isolated and dried. There was thus obtained the title compound, as a dihydrochloride salt, (0.042 g); NMR Spectrum: ($DMSOd_6$) 3.25-3.3 (m, 4H), 3.45-3.5 (m, 4H), 4.03 (s, 3H), 7.3 (s, 1H), 7.36-7.63 (m, 3H), 8.16 (s, 1H), 8.78 (s, 1H), 9.15-9.27 (br s, 2H), 10.9-11.3 (br s, 1H), 10.8 (s, 1H); Mass Spectrum: $M+H^+$ 447 and 449.

Example 34

Using an analogous procedure to that described in Example 29, except that the appropriate quinazoline-4-thiourea was reacted with ethylamine rather than with ammonia, there were obtained the 2-ethylguanidines described in Table IX.

Table IX



No.	R^6	R^7	$(R^2)_n$	Note
1	methoxy	N-methylpiperidin-4-ylmethoxy	2-chloro-6-methyl	(a)
2	methoxy	N-methylpiperidin-4-ylmethoxy	2,6-dimethyl	(b)
3	methoxy	2-morpholinoethoxy	2,6-dimethyl	(c)
4	methoxy	cyclopropylmethoxy	2,6-dimethyl	(d)

Notes

(a) The product gave the following data: NMR Spectrum: ($DMSOd_6$, 100°C) 1.31 (t, 3H), 1.36–1.47 (m, 2H), 1.74–1.84 (m, 3H), 1.95 (t, 2H), 2.2 (s, 3H), 2.33 (s, 3H), 2.79 (d, 2H), 3.57 (m, 2H), 3.72 (s, 3H), 3.99 (t, 2H), 7.06 (s, 1H), 7.29 (m, 2H), 7.41 (m, 2H), 8.35 (br s, 1H), 8.45 (s, 1H), 10.11 (br s, 1H); Mass Spectrum: $M+H^+$ 497 and 499.

(b) The product gave the following data: NMR Spectrum: ($DMSOd_6$, 100°C) 1.28 (t, 3H), 1.4 (m, 2H), 1.76 (m, 3H), 1.95 (m, 2H), 2.19 (s, 3H), 2.26 (s, 6H), 2.78 (m, 2H), 3.53 (q, 2H), 3.76 (s, 3H), 3.99 (d, 2H), 7.04 (s, 1H), 7.16 (s, 3H), 7.55 (s, 1H), 8.41 (s, 1H), 10.41 (br s, 1H); Mass Spectrum: $M+H^+$ 477.

(c) The product gave the following data: NMR Spectrum: ($DMSOd_6$, 100°C) 1.27 (t, 3H), 2.27 (s, 6H), 2.54 (m, 4H), 2.8 (t, 2H), 3.54 (m, 2H), 3.61 (t, 4H), 3.78 (s, 3H), 4.26 (t, 2H), 7.11 (s, 1H), 7.19 (s, 3H), 7.59 (s, 1H), 8.42 (s, 1H), 10.42 (br s, 1H); Mass Spectrum: $M+H^+$ 479.

(d) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 0.38 (m, 2H), 0.6 (m, 2H), 1.27 (m, 4H), 2.25 (s, 6H), 3.21 (m), 3.5 (m, 2H), 3.73 (s, 3H), 3.95 (d, 2H), 6.99 (s, 1H), 7.17 (s, 3H), 7.55 (br s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 420.

Example 35

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0

(c)	Tablet III	mg/tablet
	Compound X	1.0
	Lactose Ph.Eur	93.25
	Croscarmellose sodium	4.0
	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate	1.0

(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur	488.5
	Magnesium	1.5

(e)	Injection I		(50 mg/ml)
	Compound X		5.0% w/v
	1M Sodium hydroxide solution		15.0% v/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)		
	Polyethylene glycol 400		4.5% w/v
	Water for injection to 100%		
(f)	Injection II		(10 mg/ml)
	Compound X		1.0% w/v
	Sodium phosphate BP		3.6% w/v
	0.1M Sodium hydroxide solution		15.0% v/v
	Water for injection to 100%		
(g)	Injection III	(1mg/ml, buffered to pH6)	
	Compound X		0.1% w/v
	Sodium phosphate BP		2.26% w/v
	Citric acid		0.38% w/v
	Polyethylene glycol 400		3.5% w/v
	Water for injection to 100%		
(h)	Aerosol I		mg/ml
	Compound X		10.0
	Sorbitan trioleate		13.5
	Trichlorofluoromethane		910.0
	Dichlorodifluoromethane		490.0
(i)	Aerosol II		mg/ml
	Compound X		0.2
	Sorbitan trioleate		0.27
	Trichlorofluoromethane		70.0
	Dichlorodifluoromethane		280.0
	Dichlorotetrafluoroethane		1094.0

(j)	Aerosol III	mg/ml
	Compound X	2.5
	Sorbitan trioleate	3.38
	Trichlorofluoromethane	67.5
	Dichlorodifluoromethane	1086.0
	Dichlorotetrafluoroethane	191.6

(k)	Aerosol IV	mg/ml
	Compound X	2.5
	Soya lecithin	2.7
	Trichlorofluoromethane	67.5
	Dichlorodifluoromethane	1086.0
	Dichlorotetrafluoroethane	191.6

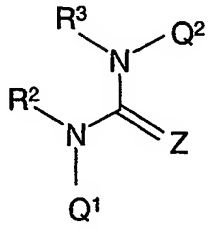
(l)	Ointment	ml
	Compound X	40 mg
	Ethanol	300 µl
	Water	300 µl
	1-Dodecylazacycloheptan-2-one	50 µl
	Propylene glycol	to 1 ml

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

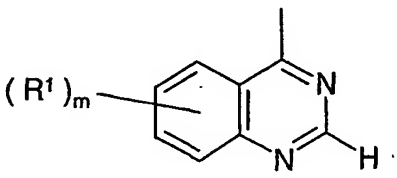
CLAIMS

1. The use of a quinazoline derivative of the Formula I

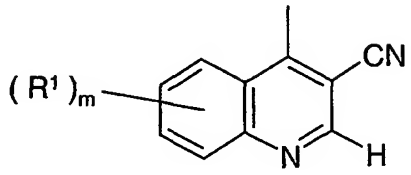


I

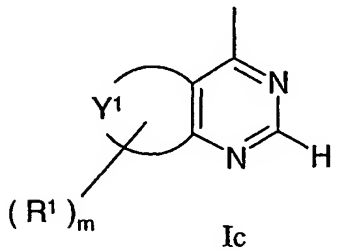
wherein Q^1 is a quinazoline-like ring such as a group of the formula Ia, Ib, Ic or Id



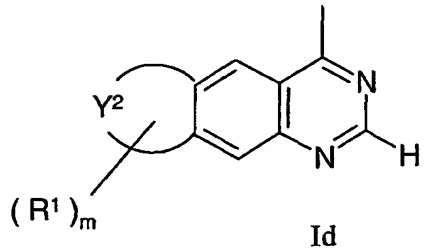
Ia



Ib



Ic



Id

wherein :

Y^1 together with the carbon atoms to which it is attached forms a 5- or 6-membered aromatic or partially unsaturated ring comprising 1 to 3 heteroatoms selected from O, N and S;

Y^2 together with the carbon atoms to which it is attached forms a 5- or 6-membered aromatic or partially unsaturated ring comprising 1 to 3 heteroatoms selected from O, N and S;

m is 0, 1, 2, 3 or 4;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl,

(1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$Q^3-X^1-$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^4-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl,

(1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3-Q^5$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^6$$

wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^6 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and any Q^6 group optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

$\mathbf{R^2}$ is hydrogen or (1-6C)alkyl and $\mathbf{R^3}$ is hydrogen or (1-6C)alkyl, or R^2 and R^3 together form a CH_2, $(CH_2)_2$ or $(CH_2)_3$ group;

Z is O, S, N(C≡N) or N(R^{11}), wherein R^{11} is hydrogen or (1-6C)alkyl; and

Q^2 is aryl, aryl-(1-3C)alkyl, aryl-(3-7C)cycloalkyl, heteroaryl, heteroaryl-(1-3C)alkyl or heteroaryl-(3-7C)cycloalkyl wherein each aryl group is phenyl or naphthyl and each heteroaryl group is a 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic heteroaryl ring containing 1 or 2 nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulphur, and

Q^2 is optionally substituted with 1, 2, 3 or 4 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^6-R^{12}$$

wherein X^6 is a direct bond or is selected from O and N(R^{13}), wherein R^{13} is hydrogen or (1-6C)alkyl, and R^{12} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^7$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, N(R^{14}), CO, CH(OR^{14}), CON(R^{14}), N(R^{14})CO, SO_2N(R^{14}), N(R^{14})SO_2, C(R^{14})$_2$O, C(R^{14})$_2$S and C(R^{14})$_2$N(R^{14}), wherein each R^{14} is hydrogen or (1-6C)alkyl, and Q^7 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or Q^2 is optionally substituted with a (1-3C)alkylenedioxy group,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on Q^2 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy,

(1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^8-R^{15}$$

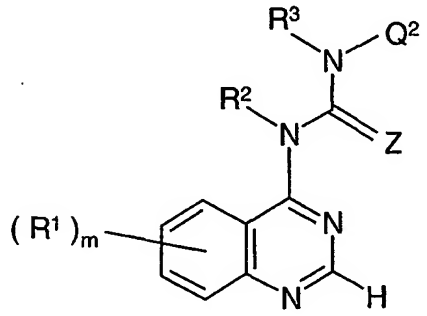
wherein X^8 is a direct bond or is selected from O and $N(R^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and R^{15} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on Q^2 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

2. The use of a quinazoline derivative of the Formula II



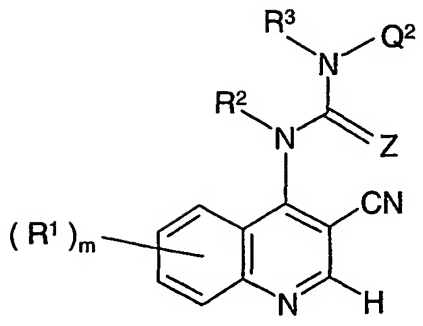
II

wherein each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined in claim 1;

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

3. The use of a quinoline derivative of the Formula III



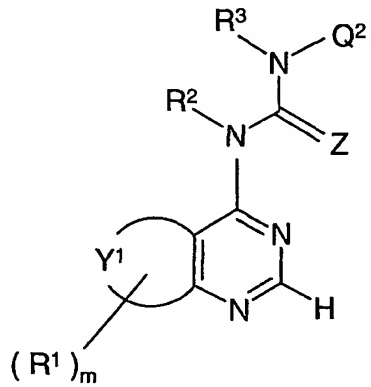
III

wherein each of m, R^1, R^2, R^3, Z and Q^2 has any of the meanings defined in claim 1;

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

4. The use of a pyrimidine derivative of the Formula IV



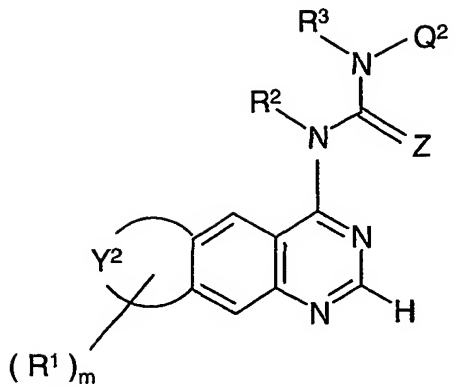
IV

wherein each of m, R^1, Y^1, R^2, R^3, Z and Q^2 has any of the meanings defined in claim 1;

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

5. The use of a quinazoline derivative of the Formula V



V

wherein each of m, R^1, Y^2, R^2, R^3, Z and Q^2 has any of the meanings defined in claim 1;

or a pharmaceutically-acceptable salt thereof;

in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

6. The use as claimed in claim 1 of a quinazoline derivative of the Formula II according to claim 2 wherein :

m is 1 and the R^1 group is located at the 6- or 7-position and is selected from methoxy, benzyloxy, cyclopropylmethoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, N-methylpyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 2-(N-methylpyrrolidin-2-yl)ethoxy, 3-pyrrolidin-2-ylpropoxy, 3-(N-methylpyrrolidin-2-yl)propoxy, 2-(2-oxoimidazolidin-1-yl)ethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-(4-aminomethylpiperidin-1-yl)propoxy, 3-(4-tert-butoxycarbonylaminopiperidin-1-yl)propoxy, 3-(4-carbamoylpiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,

2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-1-yloxy, 2-(2-morpholinoethoxy)ethoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy, 3-[N-(2-methoxyethyl)-N-methylamino]propoxy, 2-(2-methoxyethoxy)ethoxy, 3-methylamino-1-propynyl, 3-dimethylamino-1-propynyl, 3-diethylamino-1-propynyl, 6-methylamino-1-hexynyl, 6-dimethylamino-1-hexynyl, 3-(pyrrolidin-1-yl)-1-propynyl, 3-(piperidino)-1-propynyl, 3-(morpholino)-1-propynyl, 3-(4-methylpiperazin-1-yl)-1-propynyl, 6-(pyrrolidin-1-yl)-1-hexynyl, 6-(piperidino)-1-hexynyl, 6-(morpholino)-1-hexynyl, 6-(4-methylpiperazin-1-yl)-1-hexynyl, piperazin-1-yl, 4-methylpiperazin-1-yl, 3-imidazol-1-ylpropylamino, 3-pyrrolidin-1-ylpropylamino, 3-morpholinopropylamino, 3-piperidinopropylamino and 3-piperazin-1-ylpropylamino,

or m is 2 and the R^1 groups are located at the 6- and 7-positions, one R^1 group is located at the 6- or 7-position and is selected from the groups defined immediately hereinbefore and the other R^1 group is a methoxy group;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O, S, NH or N(Et); and

Q^2 is phenyl, benzyl or phenethyl which optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl and methoxy provided that at least one substituent is located at an ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

7. The use as claimed in claim 1 of a quinazoline derivative of the Formula II according to claim 2 wherein :

m is 1 and the R^1 group is located at the 7-position and is selected from 3-(1,2,3-triazol-1-yl)propoxy, 2-pyrid-4-ylethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy,

4-pyrrolidin-1-ylbut-2-en-1-yloxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-1-yloxy, 3-methylsulphonylpropoxy and 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy;

or m is 2 and one R^1 group is located at the 7-position and is selected from the groups defined immediately hereinbefore and the other R^1 group is a 6-methoxy group;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O, S, NH or N(Et); and

Q^2 is phenyl which bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl and methoxy provided that at least one substituent is located at an ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

8. The use as claimed in claim 1 of a quinazoline derivative of the Formula II according to claim 2 wherein :

m is 1 and the R^1 group is located at the 7-position and is selected from 3-(1,2,3-triazol-1-yl)propoxy, 2-pyrid-4-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, N-methylpiperidin-4-ylmethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-morpholinobut-2-en-1-yloxy, 4-morpholinobut-2-yn-1-yloxy, 3-methylsulphonylpropoxy and 2-[N-(2-methoxyethyl)-N-methylamino]ethoxy;

or m is 2 and one R^1 group is located at the 7-position and is selected from the groups defined immediately hereinbefore and the other R^1 group is a 6-methoxy group;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

Z is O; and

Q^2 is phenyl which bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, bromo and trifluoromethyl provided that at least one substituent is located at an ortho position;

or a pharmaceutically-acceptable acid-addition salt thereof.

9. A method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which

comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 01/02874

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/94 C07D215/54 C07D401/12 C07D495/04 A61K31/505
A61K31/4706 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50370 A (SUGEN) 12 November 1998 (1998-11-12) cited in the application page 69; claims	1,2,6,9
X	WO 98 38984 A (SUGEN) 11 September 1998 (1998-09-11) page 75 -page 76; claims	1,2,6,9
A	WO 98 43960 A (AMERICAN CYANAMID) 8 October 1998 (1998-10-08) cited in the application page 1; claims	1,3,6,9
A	WO 99 09024 A (SMITHKLINE) 25 February 1999 (1999-02-25) cited in the application page 1; claims	1-3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2001	09/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/GB 01/02874

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